

A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF MEDICAL DISORDERS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U. S. Application Ser. No. 60/140,345, the disclosure of
5 which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to a method for the prophylaxis and/or treatment of
10 medical disorders, and in particular proliferative and/or inflammatory skin disorders, and to
genetic molecules useful for same. The present invention is particularly directed to genetic
molecules capable of modulating growth factor interaction with its receptor on cells such as
epidermal keratinocytes to inhibit, reduce or otherwise decrease stimulation of this layer of
cells. The present invention contemplates, in a particularly preferred embodiment, a method
15 for the prophylaxis and/or treatment of psoriasis or neovascularization conditions such as
neovascularization of the retina. The present invention is further directed to the subject genetic
molecules in adjunctive therapy for epidermal hyperplasia, such as in combination with UV
treatment, and to facilitate apoptosis of cancer cells and in particular cancer cells comprising
keratinocytes.

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BACKGROUND OF THE INVENTION

Bibliographic details of the publications numerically referred to in this specification are
collected at the end of the description.

25 The reference to any prior art in this specification is not, and should not be taken as, an
acknowledgment or any form of suggestion that that prior art forms part of the common general
knowledge in Australia or any other country.

Psoriasis and other similar conditions are common and often distressing proliferative and/or
inflammatory skin disorders affecting or having the potential to affect a significant proportion

of the population. The condition arises from over proliferation of basal keratinocytes in the epidermal layer of the skin associated with inflammation in the underlying dermis. Whilst a range of treatments have been developed, none is completely effective and free of adverse side effects. Although the underlying cause of psoriasis remains elusive, there is some consensus of opinion that the condition arises at least in part from over expression of local growth factors and their interaction with their receptors supporting keratinocyte proliferation *via* keratinocyte receptors which appear to be more abundant during psoriasis.

One important group of growth factors are the dermally-derived insulin-like growth factors (IGFs) which support keratinocyte proliferation. In particular, IGF-I and IGF-II are ubiquitous peptides each with potent mitogenic effects on a broad range of cells. Molecules of the IGF type are also known as "progression factors" promoting "competent" cells through DNA synthesis. The IGFs act through a common receptor known as the Type I or IGF-I receptor, which is tyrosine kinase linked. They are synthesised in mesenchymal tissues, including the dermis, and act on adjacent cells of mesodermal, endodermal or ectodermal origin. The regulation of their synthesis involves growth hormone (GH) in the liver, but is poorly defined in most tissues [1].

Particular proteins, referred to as IGF binding proteins (IGFBPs), appear to be involved in autocrine/paracrine regulation of tissue IGF availability [2]. Six IGFBPs have so far been identified. The exact effects of the IGFBPs is not clear and observed effects *in vitro* have been inhibitory or stimulatory depending on the experimental method employed [3]. There is some evidence, however, that certain IGFBPs are involved in targeting IGF-I to its cell surface receptor.

Skin, comprising epidermis and underlying dermis, has GH receptors on dermal fibroblasts [4]. Fibroblasts synthesize IGF-I as well as IGFBPs-3, -4, -5 and -6 [5] which may be involved in targeting IGF-I to adjacent cells as well as to the overlaying epidermis. The major epidermal

cell type, the keratinocyte, does not synthesize IGF-I, but possesses IGF-I receptors and is responsive to IGF-I [6].

It is apparent, therefore, that IGF-I and other growth promoting molecules, are responsible for or at least participate in a range of skin cell activities. In accordance with the present invention, the inventors have established that aberrations in the normal functioning of these molecules or aberrations in their interaction with their receptors is an important factor in a variety of medical disorders such as proliferative and/or inflammatory skin disorders. It is proposed, therefore, to target these molecules or other molecules which facilitate their functioning or interaction with their receptors to thereby ameliorate the effects of aberrant activity during or leading to skin disease conditions and other medical conditions such as those involving neovascularization. Furthermore, these molecules may also be used to facilitate apoptosis of target cells and may be useful as adjunctive therapy for epidermal hyperplasia.

15 SUMMARY OF THE INVENTION

Nucleotide and amino acid sequences are referred to by a sequence identifier, i.e. ~~(SEQ ID NO: 1)~~ ~~(SEQ ID NO: 2)~~ ~~(SEQ ID NO: 3)~~, etc. A sequence listing is provided after the claims.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof

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capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or inflammation and/or other medical disorder.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation and/or other medical disorder.

According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to ~~SEQ ID NO. 1~~ or ~~SEQ ID NO. 2~~ wherein said catalytic domain is capable of cleaving said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell

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following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

5 Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents.

10 Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor.

Still a further aspect of the present invention contemplates an agent comprising a nucleic acid
15 molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

The present invention further contemplates the use of the genetic molecules and in particular the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor.

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BRIEF DESCRIPTION OF THE FIGURES

(SEQ ID NO. 1)

Figure 1 is a representation of the nucleotide sequence of IGFBP-2.

LOCUS HSIGFBP2 1433 bp RNA PRI 31-JAN-1990

5 DEFINITION Human mRNA for insulin-like growth factor binding protein (IGFBP-2)

ACCESSION X16302

KEYWORDS insulin-like growth factor binding protein.

SOURCE human

ORGANISM Homo sapiens

10 Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia; Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.

REFERENCE 1 (bases 1 to 1433)

AUTHORS Binkert, C., Landwehr, J., Mary, J.L., Schwander, J. and Heinrich, G.

15 TITLE Cloning, sequence analysis and expression of a cDNA encoding a novel insulin-like growth factor binding protein (IGFBP-2)

JOURNAL EMBO J. 8, 2497-2502 (1989)

STANDARD full automatic

COMMENT NCBI gi: 33009

FEATURES

20 source 1..1433

/organism="Homo sapiens"

/dev_stage="fetal"

/tissue_type="liver"

misc_feature 1416..1420

25 /note="pot. polyadenylation signal"

polyA_site 1433

/note="polyadenylation site"

CDS 118..1104

30 /note="precursor polypeptide; (AA -39 to 289); NCBI gi: 33010."

/codon_start=1

/translation="MLPRVGC PALPLPPPP LLLPLLL LLLLGASGGGGGARA EVLFR

35 CPPCTPERLAACGPPPVAPPA AVAVAGGARMPCAELVREPGCGCCSVCARLEGEACG

VYTPRCGQGLRCYPHPGSELPLQALVMGEGTCEKRRDAEYGASPEQVADNGDDHSEGG

LVENHVDSTMNMLGGGGSAGRKPLKSGMKELAVFREKVTEQHRQMKGKGGKHHLGLEEP

40 KKL RPPPARTPCQQELDQVLERISTMRLPDERGPLEHLYSLHIPNCDKHGLYNLKQCK

MSLNGQRGECWCVNPNPTGKLIQGAPTIRGDPECHLFYNEQQEACGVHTORMQ"

(<400>21)

CDS 118..234

45 /note="signal peptide; (AA -39 to -1); NCBI gi: 33011."

/codon_start=1

/translation="MLPRVGC PALPLPPPP LLLPLLL LLLLGASGGGGGARA"

(<400>22)

CDS 235..1101

/note="mature IGFBP-2; (AA 1 to 289); NCBI gi: 33012."

/codon_start=1

/translation="EVLFRCPPCTPERLAACGPPPVAPPA AVAVAGGARMPCAELVR

HUMGFIBPA Length: 2404 May 11, 1994 10:00 Type: N Check: 9946 ..

(SEQ ID No. 3)

Figure 3 is a representation of the nucleotide sequence of IGF-1-receptor.

5 LOCUS HSIGFIRR 4989 bp RNA PRI 28-MAR-1991
 DEFINITION Human mRNA for insulin-like growth factor I receptor
 ACCESSION X04434 M24599
 10 KEYWORDS glycoprotein; insulin receptor;
 insulin-like growth factor I receptor; membrane glycoprotein;
 receptor; tyrosine kinase.
 SOURCE human
 ORGANISM Homo sapiens
 Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia;
 Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
 15 REFERENCE 1 (bases 1 to 4989)
 AUTHORS Ullrich,A., Gray,A., Tam,A.W., Yang-Feng,T., Tsubokawa,M.,
 Collins,C., Henzel,W., Bon,T.L., Kathuria,S., Chen,E., Jakobs,S.,
 Francke,U., Ramachandran,J. and Fujita-Yamaguchi,Y.
 20 TITLE Insulin-like growth factor I receptor primary structure: comparison
 with insulin receptor suggests structural dererminants that define
 functional specificity
 JOURNAL EMBO J. 5, 2503-2512 (1986)
 STANDARD full automatic
 25 COMMENT NCBI gi: 33058
 FEATURES Location/Qualifiers
 source 1. .4989
 /organism="Homo sapiens"
 /tissue_type="placenta"
 /clone_lib="(lamda)gt10"
 /clone="(lambda)IGF-1-R.85, (lambda)IGF-1-R.76"
 30 sig_peptide 32. .121
 mat_peptide 122. .4132
 /note="IGF-I receptor"
 35 misc_feature 122. .2251
 /note="alpha-subunit (AA 1 - 710)"
 misc_feature 182. .190
 /note="pot.N-linked glycosylation site (AA 21 - 23)"
 misc_feature 335. .343
 /note="pot.N-linked glycostlation site (AA 72 - 74)"
 40 misc_feature 434. .442
 /note="pot.N-linked glycostlation site (AA 105 - 107)"
 misc_feature 761. .769
 /note="pot.N-linked glycostlation site (AA 214 - 216)"
 45 misc_feature 971. .979
 /note="pot.N-linked glycostlation site (AA 284 - 286)"
 misc_feature 1280. .1288
 /note="pot.N-linked glycostlation site (AA 387 - 389)"

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5 misc_feature 1343. .1351
/note="pot.N-linked glycosylation site (AA 408 - 410)"

misc_feature 1631. .1639
/note="pot.N-linked glycosylation site (AA 504 - 506)"

5 misc_feature 1850. .1858
/note="pot.N-linked glycosylation site (AA 577 - 579)"

misc_feature 1895. .1903
/note="pot.N-linked glycosylation site (AA 592 - 594)"

10 misc_feature 1949. .1957
/note="pot.N-linked glycosylation site (AA 610 - 612)"

misc_feature 2240. .2251
/note="putative proreceptor processing site (AA 707 - 710)"

15 misc_feature 2252. .4132
/note="beta-subunit (AA 711 - 1337)"

misc_feature 2270. .2278
/note="pot.N-linked glycosylation site (AA 717 - 719)"

misc_feature 2297. .2305
/note="pot.N-linked glycosylation site (AA 726 - 728)"

20 misc_feature 2321. .2329
/note="pot.N-linked glycosylation site (AA 734 - 736)"

misc_feature 2729. .2737
/note="pot.N-linked glycosylation site (AA 870 - 872)"

25 misc_feature 2768. .2776
/note="pot.N-linked glycosylation site (AA 883 - 885)"

misc_feature 2837. .2908
/note="transmembrane region (AA 906 - 929)"

misc_feature 2918. .2926
/note="pot.N-linked glycosylation site (AA 933 - 935)"

30 misc_feature 3047. .3049
/note="pot.ATP binding site (AA 976)"

misc_feature 3053. .3055
/note="pot.ATP binding site (AA 978)"

35 misc_feature 3062. .3064
/note="pot.ATP binding site (AA 981)"

misc_feature 3128. .3130
/note="pot.ATP binding site (AA 1003)"

CDS 32. .4132
/product="IGF-I receptor"
/note="50 stops when translation attempted, frame 1, code 0"

40 BASE COUNT 1216 a 1371 c 1320 g 1082 t
ORIGIN

45 HSIGFIRR Length: 4989 May 11, 1994 12:10 Type: N Check: 133 ..

Figure 4A is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosphorothioate oligonucleotides (BP3AS2, BP3AS3 and BP3S) at 0.5 μ M and 5 μ M;

* no oligonucleotide added.

5

Figure 4B is a graphical representation of a scanning imaging densitometry of Western ligand blot (Figure 4A), showing relative band intensities of IGFBP-3 and the 24kDa IGFBP-4 after treatment with phosphorothioate oligonucleotides;

* no oligonucleotide added.

10

Figure 5A is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosphorothioate oligonucleotide BP3AS2 at 0.5 μ M compared with several control oligonucleotides at 0.5 μ M.

(a) oligonucleotide BP3AS2NS; (b) oligonucleotide BP3AS4; (c) oligonucleotide BP3AS4NS; and (untreated), no oligonucleotide added.

15

Figure 5B is a graphical representation of a scanning imaging densitometry of Western ligand blot (Figure 5A), showing relative band intensities of IGFBP-3 after treatment with phosphorothioate oligonucleotides as in Figure 5A, showing IGFBP-3 band intensities expressed as a percentage of the average band intensity from conditioned medium of cells not treated with oligonucleotide.

20

Figure 6 is a graphical representation showing inhibition of IGF-I binding by antisense oligonucleotides to IGF-I receptor. IGFR.AS: antisense; IGFR.S: sense.

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Figure 7 is a graphical representation showing inhibition of IGFBP-3 production in culture medium following initial treatment with antisense oligonucleotides once daily over a 2 day period.

Figure 8 is a graphical representation showing optimization of IGFBP-3 antisense oligonucleotide concentration as determined by relative IGFBP-3 concentration in culture medium.

5 **Figure 9** is a diagrammatic representation of a map of IGF-1 Receptor mRNA and position of target ODNs.

Figure 10 is a photographic representation showing Lipid-mediated uptake of oligonucleotide in keratinocytes. HaCaT keratinocytes were incubated for 24 hours in medium (DMEM plus 10% v/v FCS) containing fluorescently labelled ODN (R451, 30 nM) and cytofectin GSV (2 µg/ml). The cells were then transferred to ODN-free medium and fluorescence microscopy (a) and phase contrast (b) images of the cells were obtained.

15 **Figure 11** is a graphical representation of uptake (A) and toxicity (B) of ODN/lipid complexes in keratinocytes. Confluence HaCaT keratinocytes were incubated in DMEM containing fluorescently labelled ODN (R451) plus liposome over 120 hours, viewed using fluorescence microscopy and trypan blue stained and counted.

Figure 12 is a graphical representation of an IGF-1 Receptor mRNA in ODN treated (30nM) HaCaT cells (2µg/ml GSV). HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Cells were treated with ODNs complementary to the human IGF-I receptor mRNA (27, 32, 74 and 78), 2 randomised sequence ODNs (R451) and R766), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated then analysed for IGF-I receptor mRNA and GAPDH mRNA levels by RNase Protection and PhosphorImager quantitation.

(A) Electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase Protection. Molecular weight markers are shown on the right hand side. Full length probe

is shown on the left hand side (G-probe and I-probe). GAPDH protected fragments (G) are seen at 316 bases and IGF-I receptor protected fragments (I) are seen at 276 bases.

(B) Relative level of IGF-I receptor mRNA following each treatment is shown.

5

Figure 13 is a graphical representation of an IGF-1 receptor mRNA in ODN treated (30nM) HaCaT cells (2 μ g/ml GSV). Summary of IGF-I receptor ODN screening data. HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGF-I receptor mRNA and GAPDH mRNA levels by RNase protection and phosphorImager quantitation. Relative level of IGF-I receptor mRNA is shown after treatment with ODNs complementary to the human IGF-I receptor mRNA, 4 randomised sequence ODNs and liposome alone. (26-86=IGF-I receptor ODNs; R1, R4, R7 and R9 = randomised ODNs (R1=R121, R4=R451, R7=R766, R9=R961); GSV=liposome alone; UT=untreated). *indicates a significant difference in relative IGF-I receptor mRNA from GSV treated cells (n=4-10, p<0.05).

Figure 14 is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% v/v FCS. Oligodeoxynucleotide (ODN) and Cytofectin GSV (GSV, Glen Research) were mixed together in serum-free DMEM, incubated at room temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30 nM random sequence or antisense ODN and 2 μ g/ml GSV or with GSV alone in DMEM containing 10% v/v FCS with solutions replaced every 24 hours. This was followed by incubation with ODN/GSV in serum-free DMEM for 48 hours. All incubations were performed at 37°C. Wells were washed twice with 1 ml cold PBS. Serum-free DMEM containing 10⁻¹⁰M ¹²⁵I-IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at 10⁻¹⁰M to 10⁻⁷M. Cells were incubated at 4°C for 17 hours with gentle shaking then washed three times with 1 ml cold PBS and lysed in 250 μ l 0.5M

NaOH/0.1% v/v Triton X-100 at room temperature for 4 hours. Specific binding of the solubilised cell extract was measured using a γ counter.

Figure 15 is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes.

Figure 16 is a photographical representation of H & E stained sections of (A) psoriatic skin biopsy prior to grafting and (B) 49 day old psoriatic skin graft using skin from the same donor.

10

Figure 17 is a photographical representation of uptake of oligonucleotide after intradermal injection into psoriatic skin graft on a nude mouse. Psoriatic skin graft was intradermally injected with ODN (R451, 50 μ l, 10 μ M). The graft was removed and sectioned after 24 hours, then viewed using confocal microscopy.

15

Figure 18(a) is a photographical representation of Pregraft, Donor JH, Donor JH, PBS treated, 50 μ l, Donor JH, #50 treated, 50 μ l, 10 μ M.

20 **Figure 18(b)** is a photographical representation of Donor LB, pregraft, Donor LB, PBS treated (50 μ l), Donor LB, #74 treated (50 μ l, 10 μ M).

Figure 18(c) is a photographical representation of Donor PW, pregraft, Donor PW, R451 treated (50 μ l, 10 μ M), Donor LB, #74 treated (50 μ l, 10 μ M).

25

Figure 18(d) is a photographical representation of Donor GM, pregraft, Donor GB, R451 treated (50 μ l, 10 μ M), Donor GM, #27 treated (50 μ l, 10 μ M).

Figure 19(a) is a photographic representation showing Donor JH pregraft, Donor JH PBS treated 50 μ l, Donor JH #50 treated 50 μ l, 10 μ M.

Figure 19(b) is a photographic representation Donor LB pregraft, Donor LB PBS treated 50 μ l, Donor LB #74 treated 50 μ l, 10 μ M.

Figure 19(c) is a photographic representation showing Donor PW pregraft, Donor PW R451 treated 50 μ l, 10 μ M, Donor PW #74 treated 50 μ l, 10 μ M.

Figure 19(d) is a photographic representation showing Donor GM pregraft, Donor GM R451 treated 50 μ l, 10 μ M, Donor #27 treated 50 μ l, 10 μ M.

Figure 20 is a graphical representation showing suppression of psoriasis after treatment with oligonucleotide (quantification). Oligonucleotide (50 μ l, 10 μ M) was injected every two days for 20 days, as were control treatments. Skin thickness was measured by removing the skin and using computer software (MCID analysis) to measure the exact thickness of each graft. N=3-4 for each treatment. *indicates a significant difference from the pregraft value (ANOVA, P<0.05)

Figure 21 is a photographic representation of α hKi-67 immunobiological binding.

Figure 22 is a photographic representation showing penetration of oligonucleotide into human skin after topical treatment. Fluorescently labelled oligonucleotide (10 μ M R451) was applied topically after formulation with cytofectin GSV (10 μ g/ml) and viewed using confocal microscopy.

Figure 23 is a photographic representation showing penetration of oligonucleotide into human skin after application of topical gel formation. Fluorescently labelled oligonucleotide

(10 μ M R451) was applied topically after complexing with cytofectin GSV (10 μ g/ml) and formulation into 3 % methylcellulose gel. Image was obtained using confocal microscopy.

Figure 24 is a graphical representation showing IGFBP-3 mRNA.

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Figure 25(a) is a graphical representation showing IGFBP-3 mRNA in AON treated (100nM) HaCaT cells (2 μ g/ml GSV).

Figure 25(b) is a graphical representation showing IGFBP-3 mRNA levels of AON treated 10 (100nm) HaCaT cells (2 μ g/ml GSV).

Figure 25(c) is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2 μ g/ml GSV).

15 **Figure 25(d)** is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2 μ g/ml GSV).

Figure 26(a) is a graphical representation showing IGFBP-3 mRNA in ODN treated (30nM) HaCaT cells (2 μ g/ml). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, 20 dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and liposome alone. (1-24 = IGFBP-3 ODNs; R1, R4, R7 and R9 = randomised ODNs (R1 = R121, R4 = R451, R7 = R766, R9 25 R961); GS = liposome alone; UT = untreated). * indicates a significant different in relative IGFBP-3 mRNA from GSV treated cells (n = 5-8, p < 0.01), ** indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n = 5-8, p < 0.05).

Figure 26(b) is a graphical representation showing IGFBP-3 mRNA in ODN treated (100nM) HaCaT cells (2µg/ml GSV). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and liposome alone. (1-24=IGFBP-3 ODNs; R1, R4, R7 and R9 = randomised ODNs (R1-R121, R4=R451, R7=R766, R9=R961), GS=liposome alone; UT=untreated). *indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n= 6-8, p<0.01).

10

Figure 27 is a representation showing a reduction in IGF-I receptor mRNA in HaCaT cells following treatment with antisense oligonucleotides. Confluent HaCaT cells were treated every 24 h for 4 days with 2 µg/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides (#26 to #86) or random sequence oligonucleotides (R121, R451 and R766). Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA by RNase protection assay. (a). Representative RNase protection assay gel showing IGF-I receptor (*IGFR*) and GAPDH mRNA in untreated or treated HaCaT cells. In this example, a reduction in IGFR band intensity relative to GAPDH can be seen with AON #27 and #78, but not with #32, #74 or the controls (R4, R7, random oligonucleotides R451 and R766, respectively; G, GSV lipid; UT, untreated).

(b) Densitometric quantitation of IGF-I receptor mRNA (normalised to GAPDH mRNA) in HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black), random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells (UT, vertical striped bar). Each oligonucleotide was assayed in duplicate in at least two separate experiments.

Results are presented as mean ± SEM. A one-way ANOVA followed by Tukey's (▲) test was performed; ▲ indicates a significant difference between cells treated with IGF-I receptor

specific AONs and all of the control treatments ($p < 0.05$). $n=4$ except for #27 and #32 ($n=6$), #28 and #68 ($n=3$), R766 ($n=9$), and R451, GSV and untreated ($n=10$).

Figure 28 is a representation showing a reduction in total cellular IGF-I receptor protein following antisense oligonucleotide treatment. Confluent HaCaT cells were treated every 24 h for 4 days with 2 μ g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONs (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with an antibody specific for the human IGF-I receptor. (a) Duplicate treated cellular extracts showing the IGF-I receptor at the predicted size of 110 kD

(b) Densitometric quantitation of IGF-I receptor protein. Results are presented as mean \pm SEM of four different experiments each performed in duplicate. A one-way ANOVA followed by a Dunnett's test was performed; * indicates a significant difference from GSV treated cells ($p < 0.01$). GSV, GSV lipid alone; UT, untreated; R451, random sequence oligonucleotide; 64, 50, 27, IGF-I receptor-specific AONs.

Figure 29 is a representation showing a reduction in IGF-I receptor numbers on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were transfected with IGF-I receptor specific AONs #27 ($-\blacktriangle-$), #50 ($-x-$), #64 ($-\blacksquare-$), a random sequence oligonucleotide R451 ($-o-$), or treated with GSV lipid alone ($-\square-$) every 24 h for four days (untreated cells, $-\ast-$). Competition binding assays using 125 I-IGF-I and the receptor-specific analogue, des(1-3)IGF-I, were performed (inset); plotted values are means \pm standard error. The mean values were then subjected to Scatchard analysis.

25

Figure 30 is a representation showing a reduction in keratinocyte cell number following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6416, or treated with GSV lipid alone every 24 h for 2 days (UT, untreated cells). Cell number was

measured in the culture wells using a dye binding assay (Experimental protocol). Results are presented as mean \pm SD. A one-way ANOVA was performed, followed by a Tukey's multiple comparison test. \blacktriangle indicates a significant difference between cells treated with AON #64 and all of the control treatments ($p < 0.001$).

5

Figure 31 is a representation showing a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides

Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random
 10 sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed histologically. (a) Donor A graft treated with AON #50 showing epidermal thinning compared with pregraft and control (PBS) treated graft, and Donor B graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. E,
 15 epidermis; *Scale bar*, 400 μ m; all pictures are at the same magnification. (b) Mean epidermal cross-sectional area over the full width of grafts was determined by digital image analysis. Results are presented as mean \pm SEM. *Shaded bars*, control treatments: R451, random oligonucleotide sequence; *solid bars*, treatments with oligonucleotides that inhibited IGF-I receptor expression in vitro. * indicates a significant difference from the vehicle treated graft
 20 ($p < 0.01$, $n = 5-7$), + + indicates a significant difference from the random sequence (R451) treated graft ($p < 0.01$, $n = 5-7$). (c) Parakeratosis (*arrow*) was absent in grafts treated with IGF-I receptor AONs (AON #50) but persisted in pregraft and control (PBS) treated graft. *Scale bar*, 100 μ m.

25 **Figure 32** is a representation showing a reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides (a) A psoriasis lesion prior to grafting, and after grafting and treatment with IGF-I receptor specific oligonucleotide #27 (AON #27) or random sequence (R451) was immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are

indicated by a dark brown nucleus (arrows). *Scale bar, 250 mm*; all pictures are at the same magnification. (b) The same lesion prior to grafting and after oligonucleotide treatment as in (a) was subjected to in situ hybridisation with a ³⁵S-labeled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains (tiny black speckles), which are almost eliminated in the epidermis of the lesion treated with the IGF-I receptor-specific oligonucleotide #27 (AON #27). Arrows indicate the basal layer of the epidermis with dermis underneath. *Scale bar, 50 μm*.

Figure 33 is a representation showing a reduction in IGF-I receptor mRNA in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to 90% confluence in DMEM containing 10% v/v fetal calf serum were treated with 24 h for two days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially available ribonuclease protection assay kit (RPAII, Ambicon Inc, Austin, Texas). Band intensity was quantified using ImageQuant software (Molecular Dynamics, Sunnyvale, California).

Figure 34 is a representation showing a reduction in IGF-I receptor protein in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to 90% confluence in DMEM containing 10% v/v fetal calf serum were treated every 24 h for four days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells were lysed in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v glycerol, 1% v/v Triton X-100 and 100 μg/ml aprotinin on ice for 30 mins, then 30 μg of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane (Millipore, Bedford, Massachusetts). Membranes were incubated with the anti-IGF-I receptor antibody C20 (Sanra Cruz Biotechnology Inc., Santa Cruz, California, 25 ng/ml in 150 mM NaCl, 10 mM Tris-HCl, pH 7.4, 0.1% v/v Tween 20) for 1 h at room temperature and developed using the Vistra ECF western blotting kit (Amersham,

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is predicated in part on the use of molecules and in particular genetic molecules and more particularly antisense molecules to down-regulate a growth factor, its
5 receptor and/or growth factor expression facilitating sequences.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin
10 capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or inflammation and/or other medical disorder.

15 Growth factor mediated cell proliferation and inflammation are also referred to as epidermal hyperplasias and these and other medical disorders may be mediated by any number of molecules such as but not limited to IGF-I, keratinocyte growth factor (KGF), transforming growth factor- α (TGF α), tumour necrosis factor- α (TNF α), interleukin-1, -4, -6 and 8 (IL-1, IL-4, IL-6 and IL-8, respectively), basic fibroblast growth factor (bFGF) or a combination
20 of one or more of the above. The present invention is particularly described and exemplified with reference to IGF-I and its receptor (IGF-I receptor) and to IGF-I facilitating molecules, IGFBPs, since targeting these molecules according to the methods contemplated herein provides the best results to date. This is done, however, with the understanding that the present invention extends to any growth factor or cytokine-like molecule, a receptor thereof
25 or a facilitating molecule like the IGFBPs involved in skin cell proliferation such as those molecules contemplated above and/or their receptors and/or facilitating molecules therefor.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a

mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or
5 inflammation and/or other medical disorder.

The present invention is particularly described by psoriasis as the proliferative skin disorder. However, the subject invention extends to a range of proliferative and/or inflammatory skin disorders or epidermal hyperplasias such as but not limited to psoriasis, ichthyosis, pityriasis
10 rubra pilaris ("PRP"), seborrhoea, keloids, keratoses, neoplasias and scleroderma, warts, benign growths and cancers of the skin. The present invention extends to a range of other disorders such as neovascularization conditions such as but not limited to hyperneovascularization such as neovascularization of the retina, lining of the brain, skin, hyperproliferation of the inside of blood vessels, kidney disease, atherosclerotic disease,
15 hyperplasias of the gut epithelium or growth factor mediated malignancies such as IGF1-mediated malignancies.

Furthermore, down-regulation of IGF-I receptor is useful as adjunctive therapy for epidermal hyperplasia. In accordance with this aspect of the present invention it is known that IGF-I
20 receptor elicits separate intracellular signals which prevent apoptosis [19]. In keratinocytes, IGF-I receptor activation has been shown to protect UV-irradiated cells from apoptosis [20]. In another cell type, a number of IGF-I receptors expressed by the cells correlated with tumorigenicity and apoptotic resistance [21]. Consequently, in accordance with the present invention, by inactivating IGF-I receptor on cells such as epidermal keratinocytes will achieve
25 three important outcomes:

- (i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation [22]. By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is

likely to be reduced leading to an overall acceleration in normalization of the lesion and reduced carcinogenic risk.

5 (ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.

10 (iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.

15 According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical
20 analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

The UV treatment and nucleic acid molecule or its chemical analogue may be administered in any order or may be done simultaneously. This method is particularly useful in treating
25 psoriasis by combination of UV and antisense therapy. Preferably the antisense therapy is directed to the IGF-I receptor.

In a preferred embodiment, the present invention is directed to a method for ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating

5 The present invention extends to any mammal such as but not limited to humans, livestock animals (e.g. horses, sheep, cows, goats, pigs, donkeys), laboratory test animals (e.g. rabbits, mice, guinea pigs), companion animals (e.g. cats, dogs) and captive wild animals. However, the instant invention is particularly directed to proliferative and/or inflammatory skin disorders such as psoriasis in humans as well as medical disorders contemplated above.

The aspects of the subject invention instantly contemplated are particularly directed to the topical application of one or more suitable nucleic molecules capable of inhibiting, reducing or otherwise interfering with IGF-mediated cell proliferation and/or inflammation. More particularly, the nucleic acid molecule targets IGF-I interaction with its receptor.

15 Conveniently, therefore, the nucleic acid molecule is an antagonist of IGF-I interaction with its receptor. Most conveniently, the nucleic acid molecule antagonist is an antisense molecule to the IGF-I receptor, to IGF-I itself or to a molecule capable of facilitating IGF-I interaction with its receptor such as but not limited to an IGFBP.

20 Insofar as the invention relates to IGFBPs, the preferred molecules are IGFBP-2, -3, -4,
-5 and -6. The most preferred molecules are IGFBP-2 and IGFBP-3.

The nucleotide sequences of IGFBP-2 and IGFBP-3 are set forth in Figures 1-~~($\langle 400 \rangle 1$)~~ and 2-~~($\langle 400 \rangle 2$)~~, respectively. According to a particularly preferred aspect of the present invention, there is provided a nucleic acid molecule comprising at least about ten nucleotides capable of hybridising to, forming a heteroduplex or otherwise interacting with an mRNA molecule directed from a gene corresponding to a genomic form of ~~$\langle 400 \rangle 1$ and/or~~ ~~SEQ ID NO. 1 and/or SEQ ID NO. 2~~ ~~$\langle 400 \rangle 2$~~ and which thereby reduces or inhibits translation of said mRNA molecule.

Preferably, the nucleic acid molecule is at least about 15 nucleotides in length and more

preferably at least about 20-25 nucleotides in length. However, the instant invention extends to any length nucleic acid molecule including a molecule of 100-200 nucleotides in length to correspond to the full length of or near full length of the subject genes.

- 5 The nucleotide sequence of the antisense molecules may correspond exactly to a region or portion of ~~<400>1~~ or ~~<400>2~~ ^{SEQ ID NO. 1 or SEQ ID NO. 2} or may differ by one or more nucleotide substitutions, deletions and/or additions. It is a requirement, however, that the nucleic acid molecule interact with an mRNA molecule to thereby reduce its translation into active protein.

- 10 Examples of potential antisense molecules for IGFBP-2 and IGFBP-3 are those capable of interacting with sequences selected from the lists in Examples 6 and 7, respectively.

The nucleic acid molecules in the form of an antisense molecule may be linear or covalently closed circular and single stranded or partially double stranded. A double stranded molecule
15 may form a triplex with target mRNA or a target gene. The molecule may also be protected from, for example, nucleases, by any number of means such as using a nonionic backbone or a phosphorothioate linkage. A convenient nonionic backbone contemplated herein is ethylphosphotriester linkage or a 2'-O-methylribosyl derivative. A particularly useful modification modifies the DNA backbone by introducing phosphorothioate internucleotide
20 linkages. Alternatively or in addition to the pyrimidine bases are modified by inclusion of a C-5 propyne substitution which modification is proposed to enhance duplex stability [23]. The present invention extends to any chemical modification to the bases and/or RNA or DNA backbone. Reference to a "chemical analogue" of a nucleic acid molecule includes reference to a modified base, nucleotide, nucleoside or phosphate backbone.

25

Examples of suitable oligonucleotide analogues are conveniently described in Ts'O *et al* [7]. Further suitable examples of oligonucleotide analogues and chemical modifications are described in references 25 to 31.

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Alternatively, the antisense molecules of the present invention may target the IGF-I gene itself or its receptor or a multivalent antisense molecule may be constructed or separate molecules administered which target at least two or an IGFBP, IGF-I and/or IGF-I-receptor. Examples of suitable antisense molecules capable of targetting the IGF-I receptor are those capable of
 5 interacting with sequences selected from the list in Example 8. One particularly useful antisense molecule is 5'- ATCTCTCCGCTTCCTTTC -3' (~~400~~10). (SEQ ID No. 10)

Other particularly useful antisense molecules are:

- #27 UCCGGAGCCAGACUU[^] (SEQ ID No. 12)
- 10 #64 CACAGUUGCUGCAAG[^] (SEQ ID No. 13)
- #78 UCUCCGCUUCCUUUC[^] (SEQ ID No. 14)
- #28 AGCCCCCACAGCGAG[^] (SEQ ID No. 15)
- #32 GCCUUGGAGAUGAGC[^] (SEQ ID No. 16)
- #40 UAACAGAGGUCAGCA[^] (SEQ ID No. 17)
- 15 #42 GGAUCAGGGACCAGU[^] (SEQ ID No. 18)
- #46 CGGCAAGCUACACAG[^] (SEQ ID No. 19)
- #50 GGCAGGCAGGCACAC[^] (SEQ ID No. 20)

Particularly useful molecules are selected from #27, #64 and #78. In a preferred embodiment
 20 these molecules comprise a C-5 propynyl dU, dC phosphorothioate modification.

A particularly preferred embodiment of the present invention contemplates a method of ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating skin or skin capable of proliferation or cells associated with said
 25 medical disorder with an effective amount of one or more nucleic acid molecules or chemical analogues thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or ameliorating the medical disorder wherein said one or more molecules comprises a polynucleotide capable of interacting with mRNA directed from an IGF-I gene, an IGF-I receptor gene or a gene encoding an IGFBP such as IGFBP-2 and/or IGFBP-3.

Preferably, the nucleic acid molecule are antisense molecules. Particularly useful antisense molecules are: May be represented as

- #27 UCCGGAGCCAGACUU[^] (SEQ ID NO.12)
 #64 CACAGUUGCUGCAAG[^] (SEQ ID NO.13)
 5 #78 UCUCGCUUCCUUUC[^] (SEQ ID NO.14)
 #28 AGCCCCACAGCGAG[^] (SEQ ID NO.15)
 #32 GCCUUGGAGAUGAGC[^] (SEQ ID NO.16)
 #40 UAACAGAGGUCAGCA[^] (SEQ ID NO.17)
 #42 GGAUCAGGGACCAGU[^] (SEQ ID NO.18)
 10 #46 CGGCAAGCUACACAG[^] (SEQ ID NO.19)
 #50 GGCAGGCAGGCACAC[^] (SEQ ID NO.20)

Even more particularly useful molecules are selected from #27, #64 and #78.

- 15 In accordance with one aspect of the present invention the nucleic acid molecule is topically applied in aqueous solution or in conjunction with a cream, ointment, oil or other suitable carrier and/or diluent. A single application may be sufficient depending on the severity or exigencies of the condition although more commonly, multiple applications are required ranging from hourly, multi-hourly, daily, multi-daily, weekly or monthly, or in some other suitable time
 20 interval. The treatment might comprise solely the application of the nucleic acid molecule or this may be applied in conjunction with other treatments for the skin proliferation and/or inflammatory disorder being treated or for other associated conditions including microbial infection, bleeding and the formation of a variety of rashes.

- 25 As an alternative to or in conjunction with antisense therapy, the subject invention extends to the nucleic acid molecule as, or incorporating, a ribozyme including a minizyme to, for example, IGF-I, its receptor or to molecules such as IGFBPs and in particular IGFBP-2 and -3. Ribozymes are synthetic nucleic acid molecules which possess highly specific endoribonuclease activity. In particular, they comprise a hybridising region which is complementary in nucleotide

sequence to at least part of a target RNA. Ribozymes are well described by Haseloff and Gerlach [8] and in International Patent Application No. WO 89/05852. The present invention extends to ribozymes which target mRNA specified by genes encoding IGF-I, its receptor or one or more IGFBPs such as IGFBP-2 and/or IGFBP-3.

5

According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to ~~(SEQ ID NO.1) or (SEQ ID NO.2)~~ ^{SEQ ID NO.1 or SEQ ID NO.2} wherein said catalytic domain is capable of cleaving

10 said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or 15 IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

20

The efficacy of the nucleic acid molecules of the present invention can be conveniently tested and screened using an *in vitro* system comprising a basal keratinocyte cell line. A particularly useful system comprises the HaCaT cell line described by Boukamp *et al* [9]. In one assay, IGF-I is added to an oligonucleotide treated HaCaT cell line. Alternatively, growth of 25 oligonucleotide treated HaCaT cells is observed on a feeder layer of irradiated 3T3 fibroblasts. Using such *in vitro* assays, it is observed that antisense oligonucleotides to IGFBP-3, for example, inhibit production of IGFBP-3 by HaCaT cells. Other suitable animal models include the nude mouse/human skin graft model (15; 16) and the "flaky skin" mouse model (17; 18). In the nude mouse model, microdermatome biopsies of psoriasis lesions are taken under

local anaesthetic from volunteers then transplanted to congenital athymic (nude) mice. These transplanted human skin grafts maintain the characteristic hyperproliferating epidermis for 6-8 weeks. They are an established model for testing the efficacy of topically applied therapies for psoriasis. In the "flaky skin" mouse model, the *fsn/fsn* mutation produces mice with skin
5 resembling human psoriasis. This mouse, or another mutant mouse with a similar phenotype is a further *in vivo* model to test the efficacy of topically applied therapies for psoriasis.

Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise
10 reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents. Preferably, the nucleic acid molecule is an antisense molecule to IGF-I, the IGF-I receptor or an IGFBP such as IGFBP-2 and/or IGFBP-3 or comprises a ribozyme to one or more of these targets or is a molecule suitable for co-suppression of one or more of these targets. The composition may comprise a single species
15 of a nucleic acid molecule capable of targeting one of IGF-I, its receptor or an IGFBP, such as IGFBP-2 or IGFBP-3 or may be a multi-valent molecule capable of targeting two or more of IGF-I, its receptor or an IGFBP, such as IGFBP-2 and/or IGFBP-3.

The nucleic acid molecules may be administered in dispersions prepared in creams, ointments,
20 oil or other suitable carrier and/or diluent such as glycerol, liquid polyethylene glycols and/or mixtures thereof. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for topical use include sterile aqueous solutions (where water
25 soluble) or dispersions and powders for the extemporaneous preparation of topical solutions or dispersions. In all cases, the form is preferably sterile although this is not an absolute requirement and is stable under the conditions of manufacture and storage. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures

thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganism can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

Topical solutions are prepared by incorporating the nucleic acid molecule compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by where necessary filter sterilization.

The active agent may alternatively be administered by intravenous, subcutaneous, nasal drip, suppository, implant means amongst other suitable routes of administration including intraperitoneal, intramuscular, absorption through epithelial or mucocutaneous linings for example via nasal, oral, vaginal, rectal or gastrointestinal administration. Reference may conveniently be made to reference 24.

As used herein "pharmaceutically acceptable carriers and/or diluents" include any and all solvents, dispersion media, aqueous solutions, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the pharmaceutical compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. Conveniently, the nucleic acid molecules of the present invention are stored in freeze-dried form and are reconstituted prior to use.

Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor. The proliferative and/or

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inflammatory skin disorder is generally psoriasis or other medical disorders as described above and the nucleic acid molecule targets IGF-I, the IGF-I receptor and/or an IGFBP such as IGFBP-2 and/or IGFBP-3.

- 5 Still a further aspect of the present invention contemplates an agent comprising a nucleic acid molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

- 10 The present invention further contemplates the use of the genetic molecules and in particular the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor. Such a use is appropriate for the treatment of certain cancers and as adjunct therapy for epidermal hyperplasia such as in combination with UV treatment.

The present invention is further described by the following non-limiting Examples.

15

15

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- 33 -

Separated proteins were electrophoretically transferred to nitrocellulose membrane (0.45mm, Schleicher and Schuell, Dassel, Germany) in a buffer containing 25mM Tris, 192mM glycine and 20% v/v methanol. IGFBPs were then visualised by the procedure of Hossenlopp *et al* [11], using [¹²⁵I]-IGF-I, followed by autoradiography. Autoradiographs were scanned in a BioRad Model GS-670 Imaging Densitometer and band densities were determined using the Molecular Analyst program.

EXAMPLE 4

Phosphorothioate oligodeoxynucleotides were synthesised by Bresatec, Adelaide, South Australia, Australia. The following antisense sequences were used: BP3AS2, 5'- GCG CCC GCT GCA TGA CGC CTG CAA C -3' (~~400~~4), a 25mer complementary to the start codon region of the human IGFBP-3 mRNA; BP3AS3, 5'- CGG GCG GCT CAC CTG GAG CTG GCG -3' (~~400~~5), a 24mer complementary to the exon 1/intron 1 splice site; BP3AS4, 5'- AGG CGG CTG ACG GCA CTA -3' (~~400~~6), an 18mer complementary to a region of the coding sequence lacking RNA secondary structure and oligonucleotide-dimer formation (using the computer software "OLIGO for PC"). Since BP3AS4 was found to be ineffective at inhibiting IGFBP-3 synthesis, it was used as a control. The following additional control oligonucleotide sequences were used: BP3S, 5'- 'CAG GCG TCA TGC AGC GGG C -3' (~~400~~7), an 18mer sense control sequence equivalent to the start codon region; BP3AS2NS, 5'- CGG AGA TGC CGC ATG CCA GCG CAG G -3' (~~400~~8), a 25mer randomised sequence with the same GC content as BP3AS2; BP3AS4NS, 5'- GAC AGC GTC GGA GCG ATC -3' (~~400~~9), an 18mer randomised sequence with the same GC content as BP3AS4NS. Design of the oligonucleotides was based on the human IGFBP-3 cDNA sequence of Spratt *et al* [12].

25

Cells were grown to one day post confluence in 2cm² wells with daily medium changes of 0.5ml Keratinocyte-SFM, then subjected to daily medium changes of Keratinocyte-SFM for a further 4 days. Daily additions of 0.5ml fresh Keratinocyte-SFM were then continued for a further 7 days, except that at the time of medium addition, 5µl oligonucleotide in PBS was added to give

the final concentrations indicated, then the wells were shaken to mix the oligonucleotide. After the final addition, cells were incubated for 24 hours and the medium collected for assay of IGFBPs. Cells were then counted after trypsinisation in a Coulter Industrial D Counter, Coulter Bedfordshire, UK. Cell numbers after oligonucleotide treatment differed by less than 10%.

5

EXAMPLE 5

HaCaT cells secrete mainly IGFBP-3 (>95%), with the only other IGFBP detectable in HaCaT conditioned medium being IGFBP-4 (<5%). The effect on IGFBP-3 and IGFBP-4 synthesis of antisense oligonucleotides at two concentrations, 5 μ M and 0.5 μ M, was tested. Two
10 oligonucleotides were used, BP3AS2 and BP3AS3, directed against the start site and the intron 1/exon 1 splice site, respectively of the IGFBP-3 mRNA. As a control, a sense oligonucleotide corresponding to the start site was used. As shown in Figures 4A and 4B, all oligonucleotides at 5 μ M caused a significant reduction of IGFBP-3 synthesis compared with untreated cells, however, the two antisense oligonucleotides inhibited IGFBP-3 synthesis of approximately 50%
15 compared to the sense control (Figure 4B). The antisense oligonucleotide directed to the start codon appeared to be more effective of the two, the difference being more apparent at the lower concentration of 0.5 μ M. The cells of IGFBP-4 secreted by the HaCaT cells make photographic reproduction of the bands on Western ligand blots difficult, however densitometry measurements provide adequate relative quantitation. This resulted in the significant
20 observation that IGFBP-4 levels were unaffected by oligonucleotide addition to the cells, suggesting that the observed inhibitory effects on IGFBP-3 are specific.

To further investigate the inhibitory effects of the more effective of the two antisense oligonucleotides, BP3AS2, inhibition by this oligonucleotide at 0.5 μ M was compared with a
25 number of control oligonucleotides, including one antisense oligonucleotide to IGFBP-3 that had proved to be ineffective at 0.5 μ M. As shown in Figures 5A and 5B, BP3AS2 was again inhibitory, resulting in levels of IGFBP-3 of approximately 50% of the most non-specifically inhibitory control oligonucleotide, the randomised equivalent of BP3AS2. The other control oligonucleotides caused no reduction in IGFBP-3 levels at 0.5 μ M, compared to untreated cells.

Of possible significance is the fact that this control oligonucleotide, BP3AS2NS, like BP3AS2 itself, has the highest potential T_m of the three control oligonucleotides used in this experiment, enhancing the probability of non-specific base pairing with non-target mRNAs. However, the lack of inhibition of IGFBP-4 secretion by BP3AS2 suggests that this oligonucleotide is selective even compared with the most closely related protein likely to be present in this cell line.

EXAMPLE 6

Antisense oligonucleotides to IGFBP2 may be selected from molecules capable of interacting

10 with one or more of the following sense oligonucleotides:

ATTGGGGGCGAGGGA
TTCGGGGCGAGGGAG
TCGGGGCGAGGGAGG
CGGGGCGAGGGAGGA
15 GGGGCGAGGGAGGAG
GGGCGAGGGAGGAGG
GGCGAGGGAGGAGGA
GCGAGGGAGGAGGAA
CGAGGGAGGAGGAAG
20 GAGGGAGGAGGAAGA
AGGGAGGAGGAAGAA
GGGAGGAGGAAGAAG
GGAGGAGGAAGAAGC
GAGGAGGAAGAAGCG
25 AGGAGGAAGAAGCGG
GGAGGAAGAAGCGGA
GAGGAAGAAGCGGAG
AGGAAGAAGCGGAGG
GGAAGAAGCGGAGGA
30 GAAGAAGCGGAGGAG
AAGAAGCGGAGGAGG
AGAAGCGGAGGAGGC
GAAGCGGAGGAGGCG
AAGCGGAGGAGGCGG
35 AGCGGAGGAGGCGGC
GCGGAGGAGGCGGCT
CGGAGGAGGCGGCTC
GGAGGAGGCGGCTCC
GAGGAGGCGGCTCCC

AGGAGGCGGCTCCCG
GGAGGCGGCTCCCGC
GAGGCGGCTCCCGCT
AGGCGGCTCCCGCTC
GGCGGCTCCCGCTCG
GCGGCTCCCGCTCGC
CGGCTCCCGCTCGCA
GGCTCCCGCTCGCAG
GCTCCCGCTCGCAGG
CTCCCGCTCGCAGGG
TCCCGCTCGCAGGGC
CCCGCTCGCAGGGCC
CCGCTCGCAGGGCCG
CGCTCGCAGGGCCGT
GCTCGCAGGGCCGTG
CTCGCAGGGCCGTGC
TCGCAGGGCCGTGCA
CGCAGGGCCGTGCAC
GCAGGGCCGTGCACC
CAGGGCCGTGCACCT
AGGGCCGTGCACCTG
GGGCCGTGCACCTGC
GGCCGTGCACCTGCC
GCCGTGCACCTGCCC
CCGTGCACCTGCCCCG
CGTGCACCTGCCCCG
GTGCACCTGCCCCGCC
TGCACCTGCCCCGCC
GCACCTGCCCCGCCG

CACCTGCCCCGCCCGC
ACCTGCCCCGCCCGCC
CCTGCCCCGCCCGCCC
CTGCCCCGCCCGCCG
TGCCCCGCCCGCCCGC
GCCCCGCCCGCCCGCT
CCCCGCCCGCCCGCTC
CCGCCCGCCCGCTCG
CGCCCCGCCCGCTCGC
GCCCCGCCCGCTCGCT
CCCCGCCCGCTCGCTC
CCGCCCGCTCGCTCG
CGCCCCGCTCGCTCGC
GCCCCGCTCGCTCGCT
CCCCGCTCGCTCGCTC
CCGCTCGCTCGCTCG
CGCTCGCTCGCTCGC
GCTCGCTCGCTCGCC
CTCGCTCGCTCGCCC
TCGCTCGCTCGCCCCG
CGCTCGCTCGCCCCGC
GCTCGCTCGCCCCGCC
CTCGCTCGCCCCGCCG
TCGCTCGCCCCGCCCG
GCTCGCCCCGCCCGCG
CTCGCCCCGCCCGGCC
TCGCCCCGCCCGCCG
CGCCCCGCCCGCCCGC

5 GCGCGCGCGCGCGCTGC
 CCGCGCGCGCGCTGCC
 CGCGCGCGCGCTGCCG
 GCGCGCGCGCTGCCGA
 CGCGCGCGCTGCCGAC
 10 GCGCGCGCTGCCGACC
 CCGCGCTGCCGACCG
 CGCGCTGCCGACCGC
 GCGCTGCCGACCGCC
 CGCTGCCGACCGCCA
 15 GCTGCCGACCGCCAG
 CTGCCGACCGCCAGC
 TGCCGACCGCCAGCA
 GCCGACCGCCAGCAT
 CCGACCGCCAGCATG
 20 CGACCGCCAGCATGCG
 GACCGCCAGCATGCT
 ACCGCCAGCATGCTG
 CCGCCAGCATGCTGC
 CGCCAGCATGCTGCC
 25 GCCAGCATGCTGCCG
 CCAGCATGCTGCCGA
 CAGCATGCTGCCGAG
 AGCATGCTGCCGAGA
 GCATGCTGCCGAGAG
 30 CATGCTGCCGAGAGT
 ATGCTGCCGAGAGTG
 TGCTGCCGAGAGTGG
 GCTGCCGAGAGTGGG
 CTGCCGAGAGTGGGC
 35 TGCCGAGAGTGGGCT
 GCCGAGAGTGGGCTG
 CCGAGAGTGGGCTGC
 CGAGAGTGGGCTGCC
 GAGAGTGGGCTGCC
 40 AGAGTGGGCTGCCCC
 GAGTGGGCTGCCCCG
 AGTGGGCTGCCCCGC
 GTGGGCTGCCCCGCG
 TGGGCTGCCCCGCGC

GGGCTGCCCCGCGCT
 GGCTGCCCCGCGCTG
 GCTGCCCCGCGCTGC
 CTGCCCCGCGCTGCC
 TGCCCCGCGCTGCCG
 GCCCCGCGCTGCCGC
 CCCCCGCGCTGCCGCT
 CCGCGCTGCCGCTG
 CCGCGCTGCCGCTGC
 CGCGCTGCCGCTGCC
 GCGCTGCCGCTGCCG
 CGCTGCCGCTGCCGC
 CTGCCGCTGCCGCCG
 TGCCGCTGCCGCCG
 GCCGCTGCCGCCGCG
 CCGCTGCCGCCGCCG
 CGCTGCCGCCGCCGC
 GCTGCCGCCGCCGCC
 CTGCCGCCGCCGCCG
 TGCCGCCGCCGCCGC
 GCCGCCGCCGCCGCT
 CCGCCGCCGCCGCTG
 CGCCGCCGCCGCTGC
 GCCGCCGCCGCTGCT
 CCGCCGCCGCTGCTG
 CGCCGCCGCTGCTGC
 CCGCCGCCGCTGCTG
 CGCCGCCGCTGCTGC
 GCGCCGCCGCTGCTG
 CTGCTGCCGCTGCTG
 TGCTGCCGCTGCTGC
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SUB A)
CMT

00123014225550

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CCCAGCTGCAGATGC
CCAGCTGCAGATGCC
CAGCTGCAGATGCCA
AGCTGCAGATGCCAC
GCTGCAGATGCCACA
CTGCAGATGCCACAC
TGCAGATGCCACACC
GCAGATGCCACACCT
CAGATGCCACACCTG
AGATGCCACACCTGC
GATGCCACACCTGCT
ATGCCACACCTGCTC
TGCCACACCTGCTCC
GCCACACCTGCTCCT
CCACACCTGCTCCTT
CACACCTGCTCCTTC
ACACCTGCTCCTTCT
CACCTGCTCCTTCTT
ACCTGCTCCTTCTTG
CCTGCTCCTTCTTGC
CTGCTCCTTCTTGCT
TGCTCCTTCTTGCTT
GCTCCTTCTTGCTTT
CTCCTTCTTGCTTTC
TCCTTCTTGCTTTCC
CCTTCTTGCTTTCCC
CTTCTTGCTTTCCCC
TTCTTGCTTTCCCCG
TCTTGCTTTCCCCGG
CTTGCTTTCCCCGGG
TTGCTTTCCCCGGGG
TGCTTTCCCCGGGGG
GCTTTCCCCGGGGGA
CTTTCCCCGGGGGAG
TTTCCCCGGGGGAGG
TTCCCCGGGGGAGGA
TCCCCGGGGGAGGAA
CCCCGGGGGAGGAAG
CCCGGGGAGGAAGG
CCGGGGGAGGAAGGG
CGGGGGAGGAAGGGG
GGGGGAGGAAGGGGG
GGGGAGGAAGGGGGT
GGGAGGAAGGGGGTT

GGAGGAAGGGGGTTG
GAGGAAGGGGGTTGT
AGGAAGGGGGTTGTG
GGAAGGGGGTTGTGG
GAAGGGGGTTGTGGT
AAGGGGGTTGTGGTC
AGGGGGTTGTGGTCG
GGGGTTGTGGTCGG
GGGGTTGTGGTCGGG
GGTTGTGGTCGGGG
GTTGTGGTCGGGGAG
TTGTGGTCGGGGAGC
TGTGGTCGGGGAGCT
GTGGTCGGGGAGCTG
TGGTCGGGGAGCTGG
GGTCGGGGAGCTGGG
GTCGGGGAGCTGGGG
TCGGGGAGCTGGGGT
CGGGGAGCTGGGGTA
GGGAGCTGGGGTAC
GGGAGCTGGGGTACA
GGAGCTGGGGTACAG
GAGCTGGGGTACAGG
AGCTGGGGTACAGGT
GCTGGGGTACAGGTT
CTGGGGTACAGGTTT
TGGGGTACAGGTTTG
GGGGTACAGGTTTGG
GGGTACAGGTTTGGG
GGTACAGGTTTGGGG
GTACAGGTTTGGGGA
TACAGGTTTGGGGAG
ACAGGTTTGGGGAGG
CAGGTTTGGGGAGGG
AGGTTTGGGGAGGGG
GGTTTGGGGAGGGGG
GTTTGGGGAGGGGGA
TTTGGGGAGGGGGAAG
TTGGGGAGGGGGAAGA
TGGGGAGGGGGAAGA
GGGGAGGGGGAAGAG
GGGAGGGGGAAGAGA
GGAGGGGGAAGAGAA

GAGGGGGAAGAGAAA
AGGGGGAAGAGAAAT
GGGGGAAGAGAAATT
GGGGGAAGAGAAATTT
GGGAAGAGAAATTTT
GGAAGAGAAATTTTT
GAAGAGAAATTTTTA
AAGAGAAATTTTTAT
AGAGAAATTTTTATT
GAGAAATTTTTATTT
AGAAATTTTTATTTT
GAAATTTTTATTTTT
AAATTTTTATTTTTG
AATTTTTATTTTTGA
ATTTTTATTTTTGAA
TTTTTATTTTTGAAC
TTTTATTTTTGAACC
TTTATTTTTGAACCC
TTATTTTTGAACCCC
TATTTTTGAACCCCT
ATTTTTGAACCCCTG
TTTTTGAACCCCTGT
TTTTGAACCCCTGTG
TTTGAACCCCTGTGT
TTGAACCCCTGTGTCC
TGAACCCCTGTGTCCC
GAACCCCTGTGTCCCT
AACCCCTGTGTCCCTT
ACCCCTGTGTCCCTTT
CCCCTGTGTCCCTTTT
CCCTGTGTCCCTTTT
CCTGTGTCCCTTTTG
CTGTGTCCCTTTTGC
TGTGTCCCTTTTGCAT
GTGTCCCTTTTGCATA
GTCCCTTTTGCATAA
TCCCTTTTGCATAAG
CCCTTTTGCATAAGA
CCTTTTGCATAAGAT
CTTTTGCATAAGATT
TTTTGCATAAGATTA
TTTGCATAAGATTAA
TTGCATAAGATTAAA

SUB A1
cont

5 TGCATAAGATTAAAG
GCATAAGATTAAAGG
CATAAGATTAAAGGA
ATAAGATTAAAGGAA
TAAGATTAAAGGAAG
AAGATTAAAGGAAGG
AGATTAAAGGAAGGA
GATTAAAGGAAGGAA
ATTAAAGGAAGGAAA
10 TTAAAGGAAGGAAAA
TAAAGGAAGGAAAAG
AAAGGAAGGAAAAGT

EXAMPLE 7

15

Antisense oligonucleotides to IGFBP3 may be selected from molecules capable of interacting with one or more of the following sense oligonucleotides:

20 CTCAGCGCCCAGCCG
TCAGCGCCCAGCCGC
CAGCGCCCAGCCGCT
AGCGCCAGCCGCTT
GCGCCCAGCCGCTTC
CGCCCAGCCGCTTCC
25 GCCCAGCCGCTTCCT
CCCAGCCGCTTCCTG
CCAGCCGCTTCCTGC
CAGCCGCTTCCTGCC
AGCCGCTTCCTGCCT
30 GCCGCTTCCTGCCTG
CCGCTTCCTGCCTGG
CGCTTCCTGCCTGGA
GCTTCCTGCCTGGAT
CTTCCTGCCTGGATT
35 TTCCTGCCTGGATT
TCCTGCCTGGATTCC
CCTGCCTGGATTCCA
CTGCCTGGATTCCAC
TGCTTCGGATTCCACA
40 GCCTGGATTCCACAG
CCTGGATTCCACAGC
CTGGATTCCACAGCT

TGGATTCCACAGCTT
GGATTCCACAGCTTC
GATTCCACAGCTTCG
ATTCCACAGCTTCGC
TTCCACAGCTTCGCG
TCCACAGCTTCGCGC
CCACAGCTTCGCGCC
CACAGCTTCGCGCCG
ACAGCTTCGCGCCGT
CAGCTTCGCGCCGTG
AGCTTCGCGCCGTGT
GCTTCGCGCCGTGTA
CTTCGCGCCGTGTAC
TTCGCGCCGTGTACT
TCGCGCCGTGTACTG
CGCGCCGTGTACTGT
GCGCCGTGTACTGTC
CGCCGTGTACTGTGCG
GCCGTGTACTGTGCGC
CCGTGTACTGTGCGCC
CGTGTACTGTGCGCC
GTGTACTGTGCGCCC
TGTACTGTGCGCCCA
GTACTGTGCGCCCAT

TACTGTCGCCCCATC
ACTGTCGCCCCATCC
CTGTCGCCCCATCCC
TGTCGCCCCATCCCT
GTCGCCCCATCCCTG
TCGCCCCATCCCTGC
CGCCCCATCCCTGCG
GCCCCATCCCTGCGC
CCCCATCCCTGCGCG
CCCATCCCTGCGCGC
CCATCCCTGCGCGCC
CATCCCTGCGCGCCC
ATCCCTGCGCGCCCA
TCCCTGCGCGCCCAG
CCCTGCGCGCCCAGC
CCTGCGCGCCCAGCC
CTGCGCGCCCAGCCT
TGCGCGCCCAGCCTG
GCGCGCCCAGCCTGC
CGCGCCCAGCCTGCC
GCGCCCAGCCTGCCA
CGCCAGCCTGCCAA
GCCCAGCCTGCCAAG
CCCAGCCTGCCAAGC

004290 42269556

SUB A2

SUB A2
Gms

007200 42365650

5 CCTGCCAAGCAGCGT
CTGCCAAGCAGCGT
TGCCAAGCAGCGTGC
GCCAAGCAGCGTGCC
CCAAGCAGCGTGCCC
10 CAAGCAGCGTGCCCC
AAGCAGCGTGCCCCG
AGCAGCGTGCCCCG
GCAGCGTGCCCCGGT
CAGCGTGCCCCGGTT
15 AGCGTGCCCCGGTTG
GCGTGCCCCGGTTGC
CGTGCCCCGGTTGCA
GTGCCCCGGTTGCAG
TGCCCCGGTTGCAGG
20 GCCCCGGTTGCAGGC
CCCCGGTTGCAGGCG
CCCGTTGCAGGCGT
CCGTTGCAGGCGTC
CGTTGCAGGCGTCA
25 GGTTCAGGCGTCAT
GTTGCAGGCGTCATG
TTGCAGGCGTCATGC
TGCAGGCGTCATGCA
GCAGGCGTCATGCAG
30 CAGGCGTCATGCAGC
AGGCGTCATGCAGCG
GGCGTCATGCAGCGG
GCGTCATGCAGCGGG
CGTCATGCAGCGGGC
35 GTCATGCAGCGGGCG
TCATGCAGCGGGCGC
CATGCAGCGGGCGCG
ATGCAGCGGGCGCGA
TGCAGCGGGCGCGAC
40 GCAGCGGGCGCGACC
CAGCGGGCGCGACCC
AGCGGGCGCGACCCA
GCGGGCGCGACCCAC
CGGGCGCGACCCACG

GGGCGCGACCCACGC
GGCGCGACCCACGCT
GCGCGACCCACGCTC
CGCGACCCACGCTCT
GCGACCCACGCTCTG
CGACCCACGCTCTGG
GACCCACGCTCTGGG
ACCCACGCTCTGGGC
CCCACGCTCTGGGCC
CCACGCTCTGGGCCG
CACGCTCTGGGCCCG
ACGCTCTGGGCCGCT
CGCTCTGGGCCGCTG
GCTCTGGGCCGCTGC
CTCTGGGCCGCTGCG
TCTGGGCCGCTGCGC
CTGGGCCGCTGCGCT
TGGGCCGCTGCGCTG
GGGCCGCTGCGCTGA
GGCCGCTGCGCTGAC
GCCGCTGCGCTGACT
CCGCTGCGCTGACTC
CGCTGCGCTGACTCT
GCTGCGCTGACTCTG
CTGCGCTGACTCTGC
TGCGCTGACTCTGCT
GCGCTGACTCTGCTG
CGCTGACTCTGCTGG
GCTGACTCTGCTGGT
CTGACTCTGCTGGTG
TGACTCTGCTGGTGC
GACTCTGCTGGTGCT
ACTCTGCTGGTGCTG
CTCTGCTGGTGCTGC
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CTGCTGGTGCTGCTC
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TGCTGCTCCGCGGGC
GCTGCTCCGCGGGCC

CTGCTCCGCGGGCCG
TGCTCCGCGGGCCGC
GCTCCGCGGGCCGCC
CTCCGCGGGCCGCCG
TCCGCGGGCCGCCGG
CCGCGGGCCGCCGGT
CGCGGGCCGCCGGTG
GCGGGCCGCCGGTG
CGGGCCGCCGGTGCC
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GGCCGCCGGTGCGC
GCCGCCGGTGCGCG
CCGCCGGTGCGCGG
CGCCGGTGCGCGGG
GCCGGTGCGCGGGC
CCGGTGCGCGGGCT
CGGTGGCGCGGGCTG
GGTGGCGCGGGCTGG
GTGGCGCGGGCTGGC
TGGCGCGGGCTGGCG
GGCGCGGGCTGGCGC
GCGCGGGCTGGCGCG
CGCGGGCTGGCGCGA
GCGGGCTGGCGCGAG
CGGGCTGGCGCGAGC
GGCTGGCGCGAGCTC
GCTGGCGCGAGCTCG
CTGGCGCGAGCTCGG
TGGCGCGAGCTCGGG
GGCGCGAGCTCGGGG
GCGCGAGCTCGGGGG
GCGAGCTCGGGGGG
CGAGCTCGGGGGGCT
GAGCTCGGGGGGCTT
AGCTCGGGGGGCTTG
GCTCGGGGGGCTTGG
CTCGGGGGGCTTGGG
TCGGGGGGCTTGGGT
CGGGGGGCTTGGGT
GGGGGGCTTGGGTCC
GGGGGCTTGGGTCCC
GGGGCTTGGGTCCCG

SUB A2
CONT

001200 420000

5 GGGCTTGGGTCCCGT
GGCTTGGGTCCCGTG
GCTTGGGTCCCGTGG
CTTGGGTCCCGTGGT
TGGGTCCCGTGGTG
TGGGTCCCGTGGTG
GGGTCCCGTGGTGCG
GGTCCCGTGGTGCGC
GTCCCGTGGTGCGCT
10 TCCCGTGGTGCGCTG
CCCCTGGTGCGCTGC
CCGTGGTGCGCTGCG
CGTGGTGCGCTGCGA
GTGGTGCGCTGCGAG
15 TGGTGCGCTGCGAGC
GGTGCGCTGCGAGCC
GTGCGCTGCGAGCCG
TGCGCTGCGAGCCGT
GCGCTGCGAGCCGTG
20 CGCTGCGAGCCGTGC
GCTGCGAGCCGTGCG
CTGCGAGCCGTGCGA
TGCGAGCCGTGCGAC
GCGAGCCGTGCGACG
25 CGAGCCGTGCGACGC
GAGCCGTGCGACGCG
AGCCGTGCGACGCGC
GCCGTGCGACGCGCG
CCGTGCGACGCGCGT
30 CGTGCGACGCGCGTG
GTGCGACGCGCGTGC
TGCGACGCGCGTGCA
GCGACGCGCGTGCA
CGACGCGCGTGCACT
35 GACGCGCGTGCACTG
ACGCGCGTGCACTGG
CGCGCGTGCACTGGC
GCGCGTGCACTGGCC
CGCGTGCACTGGCCC
40 GCGTGCACTGGCCCA
CGTGCACTGGCCAG
GTGCACTGGCCAGT
TGCACTGGCCAGTG
GCACTGGCCAGTG

CACTGGCCCAGTGCG
ACTGGCCCAGTGCGC
CTGGCCCAGTGCGCG
TGGCCCAGTGCGCGC
GGCCCAGTGCGCGCC
GCCCAGTGCGCGCCT
CCCAGTGCGCGCCTC
CCAGTGCGCGCCTCC
CAGTGCGCGCCTCCG
AGTGCGCGCCTCCGC
GTGCGCGCCTCCGCC
TGCGCGCCTCCGCC
GCGCGCCTCCGCCCG
CGCGCCTCCGCCCGC
GCGCCTCCGCCCGCC
CGCCTCCGCCCGCCG
GCCTCCGCCCGCCGT
CCTCCGCCCGCCGTG
CTCCGCCCGCCGTGT
TCCGCCCGCCGTGTG
CCGCCCGCCGTGTGC
CGCCCGCCGTGTGCG
GCCCGCCGTGTGCGC
CCCGCCGTGTGCGCG
CCGCCGTGTGCGCGG
CGCCGTGTGCGCGGA
GCCGTGTGCGCGGAG
CCGTGTGCGCGGAGC
CGTGTGCGCGGAGCT
GTGTGCGCGGAGCTG
TGTGCGCGGAGCTGG
GTGCGCGGAGCTGGT
TGCGCGGAGCTGGTG
GCGCGGAGCTGGTGC
CGCGGAGCTGGTGCG
CGGAGCTGGTGCGCG
GGAGCTGGTGCGCGA
GAGCTGGTGCGCGAG
AGCTGGTGCGCGAGC
GCTGGTGCGCGAGCC
CTGGTGCGCGAGCCG
TGGTGCGCGAGCCGG
GGTGCGCGAGCCGGG

GTGCGCGAGCCGGGC
TGCGCGAGCCGGGCT
GCGCGAGCCGGGCTG
CGCGAGCCGGGCTGC
GCGAGCCGGGCTGCG
CGAGCCGGGCTGCGG
GAGCCGGGCTGCGGC
AGCCGGGCTGCGGCT
GCCGGGCTGCGGCTG
CCGGGCTGCGGCTGC
CGGGCTGCGGCTGCT
GGGCTGCGGCTGCTG
GGCTGCGGCTGCTGC
GCTGCGGCTGCTGCC
CTGCGGCTGCTGCCT
TGCGGCTGCTGCCTG
GCGGCTGCTGCCTGA
CGGCTGCTGCCTGAC
GGCTGCTGCCTGACG
GCTGCTGCCTGACGT
CTGCTGCCTGACGTG
TGCTGCCTGACGTGC
GCTGCCTGACGTGCG
CTGCCTGACGTGCGC
TGCTGACGTGCGCA
GCCTGACGTGCGCAC
CCTGACGTGCGCACT
CTGACGTGCGCACTG
TGACGTGCGCACTGA
GACGTGCGCACTGAG
ACGTGCGCACTGAGC
CGTGCGCACTGAGCG
GTGCGCACTGAGCGA
TGCGCACTGAGCGAG
GCGCACTGAGCGAGG
CGCACTGAGCGAGGG
GCACTGAGCGAGGGC
CACTGAGCGAGGGCC
ACTGAGCGAGGGCCA
CTGAGCGAGGGCCAG
TGAGCGAGGGCCAGC
GAGCGAGGGCCAGCC
AGCGAGGGCCAGCCG
GCGAGGGCCAGCCGT

SUBAZ
CONT

[illegible]

CGAGGGCCAGCCGTG
GAGGGCCAGCCGTGC
AGGGCCAGCCGTGCG
GGGCCAGCCGTGCGG
5 GGCCAGCCGTGCGGC
GCCAGCCGTGCGGCA
CCAGCCGTGCGGCAT
CAGCCGTGCGGCATC
AGCCGTGCGGCATCT
10 GCCGTGCGGCATCTA
CCGTGCGGCATCTAC
CGTGCGGCATCTACA
GTGCGGCATCTACAC
TGCGGCATCTACACC
15 GCGGCATCTACACCG
CGGCATCTACACCGA
GGCATCTACACCGAG
GCATCTACACCGAGC
CATCTACACCGAGCG
20 ATCTACACCGAGCGC
TCTACACCGAGCGCT
CTACACCGAGCGCTG
TACACCGAGCGCTGT
ACACCGAGCGCTGTG
25 CACCGAGCGCTGTGG
ACCGAGCGCTGTGGC
CCGAGCGCTGTGGCT
CGAGCGCTGTGGCTC
GAGCGCTGTGGCTCC
30 AGCGCTGTGGCTCCG
GCGCTGTGGCTCCGG
CGCTGTGGCTCCGGC
GCTGTGGCTCCGGCC
CTGTGGCTCCGGCCT
35 TGTGGCTCCGGCCTT
GTGGCTCCGGCCTTC
TGGCTCCGGCCTTCG
GGCTCCGGCCTTCGC
GCTCCGGCCTTCGCT
40 CTCCGGCCTTCGCTG
TCCGGCCTTCGCTGC
CCGGCCTTCGCTGCC
CGGCCTTCGCTGCCA
GGCCTTCGCTGCCAG

GCCTTCGCTGCCAGC
CCTTCGCTGCCAGCC
CTTCGCTGCCAGCCG
TTCGCTGCCAGCCGT
TCGCTGCCAGCCGTC
CGCTGCCAGCCGTG
GCTGCCAGCCGTGCG
CTGCCAGCCGTGCCC
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GCCAGCCGTGCCCCG
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CAGCCGTGCCCCGAC
AGCCGTGCCCCGACG
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CGTGCCCCGACGAGG
GTGCCCCGACGAGGC
TCGCCCCGACGAGGCG
CGCCCCGACGAGGCGC
GCCCGACGAGGCGCG
CCCGACGAGGCGCGA
CCGACGAGGCGCGAC
CGACGAGGCGCGACC
GACGAGGCGCGACCG
ACGAGGCGCGACCGC
CGAGGCGCGACCGCT
GAGGCGCGACCGCTG
AGGCGCGACCGCTGC
GGCGCGACCGCTGCA
GCGCGACCGCTGCAG
CGCGACCGCTGCAGG
GCGACCGCTGCAGGC
CGACCGCTGCAGGCG
GACCGCTGCAGGCGC
ACCGCTGCAGGCGCT
CCGCTGCAGGCGCTG
CGCTGCAGGCGCTGC
GCTGCAGGCGCTGCT
CTGCAGGCGCTGCTG
TGCAGGCGCTGCTGG
GCAGGCGCTGCTGGA
CAGGCGCTGCTGGAC
AGGCGCTGCTGGACG
GGCGCTGCTGGACGG

CGCGCTGCTGGACGGGC
CGCTGCTGGACGGCC
GCTGCTGGACGGCCG
CTGCTGGACGGCCGC
TGCTGGACGGCCGCG
GCTGGACGGCCGCGG
CTGGACGGCCGCGGG
TGGACGGCCGCGGGC
GGACGGCCGCGGGCT
GACGGCCGCGGGCTC
ACGGCCGCGGGCTCT
CGGCCGCGGGCTCTG
GGCCGCGGGCTCTGC
GCCGCGGGCTCTGCG
CCGCGGGCTCTGCGT
CGCGGGCTCTGCGTC
GCGGGCTCTGCGTCA
CGGGCTCTGCGTCAA
GGGCTCTGCGTCAAC
GGCTCTGCGTCAACG
GCTCTGCGTCAACGC
CTCTGCGTCAACGCT
TCTGCGTCAACGCTA
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TGCGTCAACGCTAGT
GCGTCAACGCTAGTG
CGTCAACGCTAGTGC
GTCAACGCTAGTGCC
TCAACGCTAGTGCCG
CAACGCTAGTGCCGT
AACGCTAGTGCCGTC
ACGCTAGTGCCGTCA
CGCTAGTGCCGTGAG
GCTAGTGCCGTGAGC
CTAGTGCCGTGAGCC
TAGTGCCGTGAGCCG
AGTGCCGTGAGCCGC
GTGCGTCAAGCCGCC
TGCCGTCAAGCCGCCT
GCCGTCAAGCCGCCTG
CCGTCAAGCCGCCTGC
CGTCAAGCCGCCTGCG
GTCAGCCGCCTGCGC
TCAGCCGCCTGCGCG

SUB A2
CONT.

1. *Study the text carefully and identify the main points.*
 2. *Summarize the text in your own words.*
 3. *Identify the key words and phrases.*
 4. *Discuss the text with your partner.*
 5. *Write a short paragraph about the text.*
 6. *Prepare a presentation on the text.*
 7. *Make a poster about the text.*
 8. *Write a letter to the author.*
 9. *Draw a picture related to the text.*
 10. *Act out a scene from the text.*
 11. *Write a story inspired by the text.*
 12. *Make a video about the text.*
 13. *Write a song about the text.*
 14. *Make a game about the text.*
 15. *Write a poem about the text.*
 16. *Make a model related to the text.*
 17. *Write a report about the text.*
 18. *Make a chart about the text.*
 19. *Write a letter to the editor.*
 20. *Make a presentation on the text.*
 21. *Write a story inspired by the text.*
 22. *Make a video about the text.*
 23. *Write a song about the text.*
 24. *Make a game about the text.*
 25. *Write a poem about the text.*
 26. *Make a model related to the text.*
 27. *Write a report about the text.*
 28. *Make a chart about the text.*
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 33. *Write a song about the text.*
 34. *Make a game about the text.*
 35. *Write a poem about the text.*
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 37. *Write a report about the text.*
 38. *Make a chart about the text.*
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 42. *Make a video about the text.*
 43. *Write a song about the text.*
 44. *Make a game about the text.*
 45. *Write a poem about the text.*
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 47. *Write a report about the text.*
 48. *Make a chart about the text.*
 49. *Write a letter to the editor.*
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 51. *Write a story inspired by the text.*
 52. *Make a video about the text.*
 53. *Write a song about the text.*
 54. *Make a game about the text.*
 55. *Write a poem about the text.*
 56. *Make a model related to the text.*
 57. *Write a report about the text.*
 58. *Make a chart about the text.*
 59. *Write a letter to the editor.*
 60. *Make a presentation on the text.*
 61. *Write a story inspired by the text.*
 62. *Make a video about the text.*
 63. *Write a song about the text.*
 64. *Make a game about the text.*
 65. *Write a poem about the text.*
 66. *Make a model related to the text.*
 67. *Write a report about the text.*
 68. *Make a chart about the text.*
 69. *Write a letter to the editor.*
 70. *Make a presentation on the text.*
 71. *Write a story inspired by the text.*
 72. *Make a video about the text.*
 73. *Write a song about the text.*
 74. *Make a game about the text.*
 75. *Write a poem about the text.*
 76. *Make a model related to the text.*
 77. *Write a report about the text.*
 78. *Make a chart about the text.*
 79. *Write a letter to the editor.*
 80. *Make a presentation on the text.*
 81. *Write a story inspired by the text.*
 82. *Make a video about the text.*
 83. *Write a song about the text.*
 84. *Make a game about the text.*
 85. *Write a poem about the text.*
 86. *Make a model related to the text.*
 87. *Write a report about the text.*
 88. *Make a chart about the text.*
 89. *Write a letter to the editor.*
 90. *Make a presentation on the text.*
 91. *Write a story inspired by the text.*
 92. *Make a video about the text.*
 93. *Write a song about the text.*
 94. *Make a game about the text.*
 95. *Write a poem about the text.*
 96. *Make a model related to the text.*
 97. *Write a report about the text.*
 98. *Make a chart about the text.*
 99. *Write a letter to the editor.*
 100. *Make a presentation on the text.*

CAGCCGCCTGCGCGC
 AGCCGCCTGCGCGCC
 GCCGCCTGCGCGCCT
 CCGCCTGCGCGCCTA
 5 CGCCTGCGCGCCTAC
 GCCTGCGCGCCTACC
 CCTGCGCGCCTACCT
 CTGCGCGCCTACCTG
 TGCGCGCCTACCTGC
 10 GCGCGCCTACCTGCT
 CGCGCCTACCTGCTG
 GCGCCTACCTGCTGC
 CGCCTACCTGCTGCC
 GCCTACCTGCTGCCA
 15 CCTACCTGCTGCCAG
 CTACCTGCTGCCAGC
 TACCTGCTGCCAGCG
 ACCTGCTGCCAGCGC
 CCTGCTGCCAGCGCC
 20 CTGCTGCCAGCGCCG
 TGCTGCCAGCGCCGC
 GCTGCCAGCGCCGCC
 CTGCCAGCGCCGCCA
 TGCCAGCGCCGCCAG
 25 GCCAGCGCCGCCAGC
 CCAGCGCCGCCAGCT
 CAGCGCCGCCAGCTC
 AGCGCCGCCAGCTCC
 GCGCCGCCAGCTCCA
 30 CGCCGCCAGCTCCAG
 GCCGCCAGCTCCAGG
 CCGCCAGCTCCAGGA
 CGCCAGCTCCAGGAA
 GCCAGCTCCAGGAAA
 35 CCAGCTCCAGGAAAT
 CAGCTCCAGGAAATG
 AGCTCCAGGAAATGC
 GCTCCAGGAAATGCT
 CTCCAGGAAATGCTA
 40 TCCAGGAAATGCTAG
 CCAGGAAATGCTAGT
 CAGGAAATGCTAGTG
 AGGAAATGCTAGTGA
 GGAAATGCTAGTGAG

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AAATGCTAGTGAGTC
AATGCTAGTGAGTCG
ATGCTAGTGAGTCGG
TGCTAGTGAGTCGGA
GCTAGTGAGTCGGAG
CTAGTGAGTCGGAGG
TAGTGAGTCGGAGGA
AGTGAGTCGGAGGAA
GTGAGTCGGAGGAAG
TGAGTCGGAGGAAGA
GAGTCGGAGGAAGAC
AGTCGGAGGAAGACC
GTCGGAGGAAGACCG
TCGGAGGAAGACCGC
CGGAGGAAGACCGCA
GGAGGAAGACCGCAG
GAGGAAGACCGCAGC
AGGAAGACCGCAGCG
GGAAGACCGCAGCGC
GAAGACCGCAGCGCC
AAGACCGCAGCGCCG
AGACCGCAGCGCCGG
GACCGCAGCGCCGGC
ACCGCAGCGCCGGCA
CCGCAGCGCCGGCAG
CGCAGCGCCGGCAGT
GCAGCGCCGGCAGTG
CAGCGCCGGCAGTGT
AGCGCCGGCAGTGTG
GCGCCGGCAGTGTGG
CGCCGGCAGTGTGGA
GCCGGCAGTGTGGAG
CCGGCAGTGTGGAGA
CGGCAGTGTGGAGAG
GGCAGTGTGGAGAGC
GCAGTGTGGAGAGCC
CAGTGTGGAGAGCCC
AGTGTGGAGAGCCCC
GTGTGGAGAGCCCCG
TGTGGAGAGCCCCGT
GTGGAGAGCCCCGTCC
TGGAGAGCCCCGTCCG
GGAGAGCCCCGTCCGT

GAGAGCCCGTCCCGTC
AGAGCCCGTCCGTCT
GAGCCCGTCCGTCTC
AGCCCGTCCGTCTCC
GCCCGTCCGTCTCCA
CCCGTCCGTCTCCAG
CCGTCCGTCTCCAGC
CGTCCGTCTCCAGCA
GTCCGTCTCCAGCAC
TCCGTCTCCAGCACG
CCGTCTCCAGCACGC
CGTCTCCAGCACGCA
GTCTCCAGCACGCAC
TCTCCAGCACGCACC
CTCCAGCACGCACCG
TCCAGCACGCACCGG
CCAGCACGCACCGGG
CAGCACGCACCGGGT
AGCACGCACCGGGTG
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CACGCACCGGGTGTC
ACGCACCGGGTGTCT
CGCACCGGGTGTCTG
GCACCGGGTGTCTGA
CACCGGGTGTCTGAT
ACCGGGTGTCTGATC
CCGGGTGTCTGATCC
CGGGTGTCTGATCCC
GGGTGTCTGATCCCA
GGTGTCTGATCCCAA
GTGTCTGATCCCAAG
TGTCTGATCCCAAGT
GTCTGATCCCAAGTT
TCTGATCCCAAGTTC
CTGATCCCAAGTTCC
TGATCCCAAGTTCCA
GATCCCAAGTTCCAC
ATCCCAAGTTCCACC
TCCCAAGTTCCACCC
CCCAAGTTCCACCCC
CCAAGTTCCACCCCC
CAAGTTCCACCCCCCT
AAGTTCCACCCCCCTC
AGTTCCACCCCCCTCC

5

10

14

2

2

ATGCTAAAGACAGCC
TGCTAAAGACAGCCA
GCTAAAGACAGCCAG
CTAAAGACAGCCAGC
TAAAGACAGCCAGCG
AAAGACAGCCAGCGC
AAGACAGCCAGCGCT
AGACAGCCAGCGCTA
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SVB A2
CONT.

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TCGCCCTTCCAAAGG
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GCCCTTCCAAAGGCA

1. The first part of the paper is devoted to the study of the asymptotic behavior of the solutions of the system (1) as $t \rightarrow \infty$. It is shown that the solutions of the system (1) are bounded and tend to zero as $t \rightarrow \infty$.

40

GGACGTGCAC+GC

CAAGTTAATGTGC

SUB A2
CONT.

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SUB A2
CONT.

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GCACAGCACCCAGAC
CACAGCACCCAGACT
ACAGCACCCAGACTT
CAGCACCCAGACTTC
AGCACCCAGACTTCA
GCACCCAGACTTCAT

1. *What is the purpose of the study?*
 2. *What are the research questions or hypotheses?*
 3. *What is the study design?*
 4. *What is the sample size and how was it selected?*
 5. *What are the variables being studied?*
 6. *What are the data collection methods?*
 7. *What are the results of the study?*
 8. *What are the conclusions and implications of the study?*

4

CGAAGCGGCCGACCA
GAAGCGGCCGACCAC
AAGCGGCCGACCACT
AGCGGCCGACCACTG
GCGGCCGACCACTGA
CGGCCGACCACTGAC
GGCCGACCACTGACT
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0555274-052400

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Sub A2
Cont.

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Sub A2
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Sub A2
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Sub A2
Cust

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AATAAAGTTTTTACC
10 ATAAAGTTTTTACCA
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AAAGTTTTTACCATT

EXAMPLE 8

15

Antisense oligonucleotides to IGF-I may be selected from molecules capable of interacting with one or more of the following ~~sense oligonucleotides~~:

Sub A3

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SUB A3
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Symbol	Meaning	Symbol	Meaning
\mathcal{A}	Algebra	\mathcal{B}	Basis
\mathcal{C}	Class	\mathcal{D}	Diagram
\mathcal{E}	Entity	\mathcal{F}	Field
\mathcal{G}	Group	\mathcal{H}	Homomorphism
\mathcal{I}	Index	\mathcal{J}	Join
\mathcal{K}	Kernel	\mathcal{L}	Language
\mathcal{M}	Module	\mathcal{N}	Norm
\mathcal{O}	Order	\mathcal{P}	Operation
\mathcal{Q}	Quotient	\mathcal{R}	Relation
\mathcal{S}	Set	\mathcal{T}	Transformation
\mathcal{U}	Union	\mathcal{V}	Vector
\mathcal{W}	Weight	\mathcal{X}	Variable
\mathcal{Y}	Yield	\mathcal{Z}	Zero

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SUB A3
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	ACCTGGAGCCAGAGA	GCCTCCTCGTCCTCC	CAAGGCCGAGAACGG
	CCTGGAGCCAGAGAA	CCTCCTCGTCCTCCC	AAGGCCGAGAACGGC
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	TGGAGCCAGAGAAC	TCCTCGTCCTCCTCG	GGCCGAGAACGGCCC
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SUB A3
Cond.

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SUB A3
cont

1. *Phragmites australis* (Cav.) Trin. ex Steud.
 2. *Scirpus americanus* (L.) Pers.
 3. *Eleocharis acicularis* (L.) Rostk Schmidt
 4. *Sagittaria arifolia* (L.) Link.
 5. *Alisma plantago-foliosa* (L.) Rostk Schmidt
 6. *Sparganium angustifolium* Michx.
 7. *Najas* sp.
 8. *Chara* sp.
 9. *Utricularia* sp.
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1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2039 2040 2041 2042 2043 2044 2045 2046 2047 2048 2049 2050 2051 2052 2053 2054 2055 2056 2057 2058 2059 2060 2061 2062 2063 2064 2065 2066 2067 2068 2069 2070 2071 2072 2073 2074 2075 2076 2077 2078 2079 2080 2081 2082 2083 2084 2085 2086 2087 2088 2089 2090 2091 2092 2093 2094 2095 2096 2097 2098 2099 2100 2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2113 2114 2115 2116 2117 2118 2119 2120 2121 2122 2123 2124 2125 2126 2127 2128 2129 2130 2131 2132 2133 2134 2135 2136 2137 2138 2139 2140 2141 2142 2143 2144 2145 2146 2147 2148 2149 2150 2151 2152 2153 2154 2155 2156 2157 2158 2159 2160 2161 2162 2163 2164 2165 2166 2167 2168 2169 2170 2171 2172 2173 2174 2175 2176 2177 2178 2179 2180 2181 2182 2183 2184 2185 2186 2187 2188 2189 2190 2191 2192 2193 2194 2195 2196 2197 2198 2199 2200 2201 2202 2203 2204 2205 2206 2207 2208 2209 2210 2211 2212 2213 2214 2215 2216 2217 2218 2219 2220 2221 2222 2223 2224 2225 2226 2227 2228 2229 2230 2231 2232 2233 2234 2235 2236 2237 2238 2239 2240 2241 2242 2243 2244 2245 2246 2247 2248 2249 2250 2251 2252 2253 2254 2255 2256 2257 2258 2259 2260 2261 2262 2263 2264 2265 2266 2267 2268 2269 2270 2271 2272 2273 2274 2275 2276 2277 2278 2279 2280 2281 2282 2283 2284 2285 2286 2287 2288 2289 2290 2291 2292 2293 2294 2295 2296 2297 2298 2299 2300 2301 2302 2303 2304 2305 2306 2307 2308 2309 2310 2311 2312 2313 2314 2315 2316 2317 2318 2319 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329 2330 2331 2332 2333 2334 2335 2336 2337 2338 2339 2340 2341 2342 2343 2344 2345 2346 2347 2348 2349 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 2368 2369 2370 2371 2372 2373 2374 2375 2376 2377 2378 2379 2380 2381 2382 2383 2384 2385 2386 2387 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 2399 2400 2401 2402 2403 2404 2405 2406 2407 2408 2409 2410 2411 2412 2413 2414 2415 2416 2417 2418 2419 2420 2421 2422 2423 2424 2425 2426 2427 2428 2429 2430 2431 2432 2433 2434 2435 2436 2437 2438 2439 2440 2441 2442 2443 2444 2445 2446 2447 2448 2449 2450 2451 2452 2453 2454 2455 2456 2457 2458 2459 2460 2461 2462 2463 2464 2465 2466 2467 2468 2469 2470 2471 2472 2473 2474 2475 2476 2477 2478 2479 2480 2481 2482 2483 2484 2485 2486 2487 2488 2489 2490 2491 2492 2493 2494 2495 2496 2497 2498 2499 2500 2501 2502 2503 2504 2505 2506 2507 2508 2509 2510 2511 2512 2513 2514 2515 2516 2517 2518 2519 2520 2521 2522 2523 2524 2525 2526 2527 2528 2529 2530 2531 2532 2533 2534 2535 2536 2537 2538 2539 2540 2541 2542 2543 2544 2545 2546 2547 2548 2549 2550 2551 2552 2553 2554 2555 2556 2557 2558 2559 2560 2561 2562 2563 2564 2565 2566 2567 2568 2569 2570 2571 2572 2573 2574 2575 2576 2577 2578 2579 2580 2581 2582 2583 2584 2585 2586 2587 2588 2589 2590 2591 2592 2593 2594 2595 2596 2597 2598 2599 2600 2601 2602 2603 2604 2605 2606 2607 2608 2609 2610 2611 2612 2613 2614 2615 2616 2617 2618 2619 2620 2621 2622 2623 2624 2625 2626 2627 2628 2629 2630 2631 2632 2633 2634 2635 2636 2637 2638 2639 2640 2641 2642 2643 2644 2645 2646 2647 2648 2649 2650 2651 2652 2653 2654 2655 2656 2657 2658 2659 2660 2661 2662 2663 2664 2665 2666 2667 2668 2669 2670 2671 2672 2673 2674 2675 2676 2677 2678 2679 2680 2681 2682 2683 2684 2685 2686 2687 2688 2689 2690 2691 2692 2693 2694 2695 2696 2697 2698 2699 2700 2701 2702 2703 2704 2705 2706 2707 2708 2709 2710 2711 2712 2713 2714 2715 2716 2717 2718 2719 2720 2721 2722 2723 2724 2725 2726 2727 2728 2729 2730 2731 2732 2733 2734 2735 2736 2737 2738 2739 2740 2741 2742 2743 2744 2745 2746 2747 2748 2749 2750 2751 2752 2753 2754 2755 2756 2757 2758 2759 2760 2761 2762 2763 2764 2765 2766 2767 2768 2769 2770 2771 2772 2773 2774 2775 2776 2777 2778 2779 2780 2781 2782 2783 2784 2785 2786 2787 2788 2789 2790 2791 2792 2793 2794 2795 2796 2797 2798 2799 2800 2801 2802 2803 2804 2805 2806 2807 2808 2809 2810 2811 2

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5 TTCAATCCAAGGCTGT	AAATCCTGAACTTTC	TGTCCGGAGGCATGG
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15 GCTGTTACCATTTTA	CTTTCTCCCTCATCG	CATGGGTGAGCATGG
CTGTTACCATTTTAA	TTTCTCCCTCATCGG	ATGGGTGAGCATGGC
TGTTACCATTTTAAAC	TTCTCCCTCATCGGC	TGGGTGAGCATGGCA
GTTACCATTTTAAACG	TCTCCCTCATCGGCC	GGGTGAGCATGGCAG
TTACCATTTTAAACGC	CTCCCTCATCGGCC	GGTGAGCATGGCAGC
20 TACCATTTTAAACGCT	TCCCTCATCGGCCCG	GTGAGCATGGCAGCT
ACCATTTTAAACGCTG	CCCTCATCGGCCCGG	TGAGCATGGCAGCTG
CCATTTTAAACGCTGC	CCTCATCGGCCCGGC	GAGCATGGCAGCTGG
CATTTTAAACGCTGCC	CTCATCGGCCCGGCG	AGCATGGCAGCTGGT
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TAACGCTGCCTAATT	CGGCCCGGCGCTGAT	GGCAGCTGGTTGCTC
AACGCTGCCTAATTT	GGCCCGGCGCTGATT	GCAGCTGGTTGCTCC
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TGCCTAATTTTGCCA	GGCGCTGATTCCCTCG	TGGTTGCTCCATTTG
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[illegible]

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GGTCTTTCTCTCAGT
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SUB A3
CENT

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CTCAGTGAAGGTGGG
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5 CAGTGAAGGTGGGGA
AGTGAAGGTGGGGAG
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GAAGGTGGGGAGAAG
10 AAGGTGGGGAGAAGC
AGGTGGGGAGAAGCT
GGTGGGGAGAAGCTG
GTGGGGAGAAGCTGA
TGGGGAGAAGCTGAA
15 GGGGAGAAGCTGAAC
GGGAGAAGCTGAACC
GGAGAAGCTGAACCG
GAGAAGCTGAACCGG
AGAAGCTGAACCGGC
20

EXAMPLE 9

Sub-confluent HaCaT cells were treated as described above with phosphorothioate oligonucleotides IGFR.AS (antisense: 5'-ATCTCTCCGCTTCCTTTC-3'; ~~(SEQ ID NO. 10)~~ ~~(400-10)~~; ref 13) and IGFR.S (sense control: 5'-GAAAGGAAGCGGAGAGAT-3'; ~~(SEQ ID NO. 11)~~ ~~(400-11)~~; ref 13)
25 IGF-I binding to the cell monolayers was then measured as ¹²⁵I-IGF-I.

EXAMPLE 10

The results of this experiment are shown in Figures 7 and 8.

30 HaCaT cells were initially plated in DMEM with 10% v/v serum, then AS oligo experiments were performed in complete "Keratinocyte-SFM" (Gibco) to exclude the influence of exogenous IGFBPs. Oligos were synthesised as phosphorothioate (nuclease-resistant) derivatives (Bresatec, South Australia) and were as follows: antisense: AS2, 5'-GCGCCCGCTGCATGACGCCTGCAAC-3' ~~(SEQ ID NO. 4)~~ (IGFBP-3 start codon); controls: AS2NS, 5'-CGGAGATGCCGCATGCCAGCGCAGG-3' ~~(SEQ ID NO. 5)~~ AS4,
35

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5'-AGGCGGCTGACGGCACTA-3'^A (SEQ ID NO. 6) AS4NS, 5'-GACAGCGTCGGAGCGATC-3'^A (SEQ ID NO. 9)
 IGFAS, 5'-ATCTCTCCGCTTCCTTTC-3'^A (SEQ ID NO. 10)
 IGFAS, 5'-GAAAGGAAGCGGAGAGAT-3'^A (SEQ ID NO. 11)

Oligos to IGFBP-3 were based on the published sequence of Spratt *et al* [12]. AS oligos were added to HaCaT monolayers in 0.5ml medium in 24-well plates at the concentrations and addition frequencies indicated. IGFBP-3 measured in cell-conditioned medium using a dot-blot assay, adapted from the Western ligand blot method of Hossenlopp *et al* [11], in which 100µl of conditioned medium was applied to nitrocellulose filters with a vacuum dot-blot apparatus. After drying the membranes at 37°C, relative amounts of IGFBP are determined by ¹²⁵I-IGF-I-binding, autoradiography and computerised imaging densitometry. Triplicate wells (except in Figure 7, where duplicate wells were measured as shown) were analysed and corrected for changes in cell number per well. Relative cell number per well was determined using an amido black dye method, developed specifically for cultured monolayers of HaCaT cells [14]. Cell numbers differed by less than 10% after treatment. For oligos to the IGF receptor, receptor quantitation in intact HaCaT monolayers was by overnight incubation with ¹²⁵I-IGF-I (30,000cpm/well) at 4°C.

EXAMPLE 11

Experiments involving ribozymes are generally conducted as described in ~~International~~ ^{International} Patent Application No. WO 89/05852 and in Haselhoff and Gerlach [8]. Ribozymes are constructed with a hybridising region which is complementary in nucleotide sequence to at least part of a target RNA which, in this case, encodes IGFBP-2. Activity of ribozymes is measurable on, for example, Northern blots or using animal models such as in the nude mouse model (15; 16) or the "flaky skin" mouse model (17; 18).

EXAMPLE 12

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGFBP-3 production. The activity of the ribozymes is determined as in Example 11.

EXAMPLE 13

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

5

EXAMPLE 14

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

EXAMPLE 15

- 10 Twenty-one antisense oligonucleotides targeted to mRNA sequences encoding the IGF-1 receptor, and four random oligonucleotides were synthesized. The antisense oligonucleotides are C5-propynyl-dU, dC 15mer phosphorothioate oligodeoxyribonucleotides. In these oligonucleotides, a phosphorothioate backbone replaces the phosphodiester backbone of naturally occurring DNA. The positions of the 21 sequence specific antisense
15 oligonucleotides relative to the IGF-1 receptor mRNA structure are shown in Figure 9.

EXAMPLE 16

- Experiments were performed to determine the uptake of the antisense oligonucleotides of Example 15 into keratinocytes. Cells of the differentiated human keratinocyte cell line,
20 HaCaT, were incubated for 24 hours in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% (w/v) fetal calf serum (FCS) containing fluorescently labelled oligonucleotide (R451, a randomized sequence oligonucleotide, 30nM) and cytofectin GSV (2µg/ml, Glen Research, 44901 Falcon Place, Sterling, VA 20166, Cat. No. 70-3815-78). Cells were then transferred to oligonucleotide-free medium and fluorescence microscopy and
25 phase contrast images of the cells were obtained. Figure 10 shows fluorescence microscopy (Panel A) and phase contrast (Panel B) images of uptake of fluorescently labelled oligonucleotide in the majority of cells in a HaCaT monolayer. The degree of uptake obtained with the cationic lipid cytofectin was far greater than the uptake obtained with the next best lipid tried, Tfx-50.

A further experiment was performed to assess the uptake and toxicity associated with the use of cytofectin GSV over five days. Confluent HaCaT keratinocytes were incubated in DMEM containing fluorescently labelled oligonucleotide R451 (30nM or 100 nM) plus cytofectin GSV (2 μ g/ml or 5 μ g/ml) over 120 hours, viewed by fluorescence microscopy, tryptan blue stained, and counted. The graphs in Figure 11 depict uptake (Panel A) and toxicity (Panel B). The proportion of cells containing oligonucleotide remained high over the 120 hour period. The combination of 30 nM oligonucleotide and 2 μ g/ml GSV provided optimal uptake and minimal toxicity.

EXAMPLE 17

The twenty-one oligonucleotides of Example 15 were then screened for their ability to inhibit IGF-I receptor mRNA levels in HaCaT cells, in accordance with the teachings herein. HaCaT cells were grown to 90% confluence in DMEM supplemented with 10% (v/v) FCS. Antisense oligonucleotides (30nM) were completed with cytofectin GSV (2 μ g/ml) and added ^{to the} ~~for he~~ cells in the presence of serum. HaCaT keratinocytes were treated with the oligonucleotide/GSV complexes or randomized sequence oligonucleotides (R451, R766), liposome alone (GSV), or were left untreated (UT). Duplicate treatments were performed. Repeat additions of the oligonucleotides/GSV complex were performed at 24, 48 and 76 hours following the first addition. Total RNA was isolated as per the RNeasy protocol (Qiagen, Crawley, UK) 96 hours following the first addition.

IGF-I receptor mRNA and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA levels were simultaneously determined by a ribonuclease (RNase) protection assay. The RNase Protection Assay kit, *in vitro* transcription kit, and IGF-I receptor and GAPDH DNA templates were obtained from Ambion, Inc. (2130 Woodward St., Houston, TX 77033). The amount of IGF-I receptor mRNA in any given sample was expressed as the amount of IGF-I receptor mRNA relative to the amount of GAPDH mRNA. Each oligonucleotide was tested in at least two separate experiments.

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Figure 12 depicts representative results of the screening process. Panel A shows an electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase protection. Molecular weight markers are shown on the right hand side. The full-length probe is shown on the left hand side; G-probe indicates the IGF-I receptor probe. GAPDH protected fragments (G) are seen at 316 bases and IGF-I protected fragments (I) are seen at 276 bases. Exhibit E, Panel B provides a graph indicating the relative level of IGF-I receptor mRNA following each treatment.

The results obtaining from the above screening assays are summarized in Figure 13. The graph depicts the relative level of IGF-I receptor mRNA after treatment with oligonucleotides complementary to the human IGF-I receptor mRNA (26-86), four randomized sequence oligonucleotides (R1, R4, R7, R9), liposome alone (GSV), or no treatment (UT). Asterisks indicate a significant different in relative IGF-I receptor mRNA as compared to GSV treated cells (n=4-10, p < 0.05).

As demonstrated in Figure 13, treatment with eighteen of the twenty-one oligonucleotides resulted in a significant different in levels of IGF-I receptor mRNA relative to GSV treated cells. Three of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to less than 35% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5' to 3' direction:

#27 UCCGGAGCCAGACUUA (SEQ ID NO.12)
 #64 CACAGUUGCUGCAAG (SEQ ID NO.13)
 #78 UCUCCGCUUCCUUUA (SEQ ID NO.14)

As further demonstrated in Figure 13, six of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to between 35 and 50% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5' to 3' direction:

#28 AGCCCCCACAGCGAG^ (SEQ ID NO. 15)
#32 GCCUUGGAGAUGAGC^ (SEQ ID NO. 16)
#40 UAACAGAGGUCAGCA^ (SEQ ID NO. 17)
#42 GGAUCAGGGACCAGU^ (SEQ ID NO. 18)
5 #46 CGGCAAGCUACACAG^ (SEQ ID NO. 19)
#50 GGCAGGCAGGCACAC^ (SEQ ID NO. 20)

EXAMPLE 19

Another experiment was performed demonstrating that antisense oligonucleotides targeted to genetic sequences encoding the IGF0I receptor and that reduce IGF-I receptor mRNA levels also inhibit the IGF-I receptor level on the surface of the treated cultured keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% (v/v) FCS. Oligodeoxynucleotide and cytofectin GSV were mixed together in serum-free DMEM, and incubated at room temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30nM random sequence or antisense oligonucleotide and 2 μ m/ml GSV, or with GSV alone in DMEM containing 10% (v/v) FCS with solutions replaced every 24 hours. This was followed by incubation with oligonucleotide/GSV in serum-free DMEM for 48 hours. All incubations were performed at 37°C. Cells were washed twice with 1ml cold PBS. Serum-free DMEM containing 10⁻¹⁰M ¹²⁵I-IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at 10⁻¹¹M to 10⁻⁷M. Cells were incubated at 4°C for 17 hours with gentle shaking, then washed three times with 1ml cold PBS and lysed in 250 μ l 0.5M NaOH/0.1% (v/v) Triton X-100 at room temperature for 4 hours. Specific binding of the solubilised cell extract was measured using a gamma counter. As shown in Figure 14, treatment of HaCaT keratinocytes with oligonucleotide reduced cell surface IGF-I receptor levels to 30% of levels in untreated keratinocytes or in keratinocytes treated with liposome alone or a random oligonucleotide, R766. As shown in Figure 15, treatment with oligonucleotide #27 also significantly reduced cell surface IGF-I receptor levels relative to untreated keratinocytes or treatment with liposome alone or random nucleotide R451. As demonstrated in Example 17,

oligonucleotides #64 and #27 reduce IGF-I receptor mRNA levels in cultured keratinocytes to less than 35% of GSV-treated cells. Accordingly, the ability of an oligonucleotide to reduce IGF-I receptor mRNA levels is correlated with its ability to reduce cell surface IGF-I receptor levels.

5

The forgoing Examples demonstrate that antisense oligonucleotides targeted to the IGF-I receptor can be delivered to human keratinocytes *in vitro*, can inhibit IGF-I receptor mRNA levels in human keratinocytes *in vitro*, and that inhibition of mRNA levels is correlated with reduction of cell surface IGF-I receptor levels.

10

EXAMPLE 19

Further experiments demonstrated the efficacy of antisense oligonucleotides targeted to the IGF-I receptor in an *in vivo* model of psoriasis. An animal model of psoriasis is the human psoriatic skin xenograft model. The skin used in this model contains the true disease state.

15 In this model, reduction in epidermal thickness of psoriatic grafts in response to treatment is positively correlated with efficacy of treatment. Both normal and psoriatic human skin were

grafted
1 ~~grafted into a thymic (nude) mice in accordance with~~ a thymic (nude) mice in accordance with the methods of Baker *et al* (1992) *Brit. J. Dermatol.* 126:105 and Nanney *et al* (1992) *J. Invest. Dermatol.* 92:296. Successful grafting was achieved, as demonstrated in Figure 16,

20 which shows hemotoxylin and eosin (H&E) stained sections of a 49-day old psoriatic human skin graft (Panel B) compared to the histology of the skin graft prior to grafting (Panel A). The histological features of psoriasis present in the pregraft section (e.g., parakeratosis, acanthosis and pronounced rete ridges) are present in the grafts more than seven weeks post grafting.

25

Using the model, oligonucleotide uptake was measured in epidermal keratinocytes *in vivo* after intradermal injection. Fluorescently labelled oligonucleotide (R451, 50 μ l, 10 μ M injection) was intradermally injected into psoriatic and normal skin grafts on a thymic mice. Live confocal microscopy and fluorescence microscopy of fixed sections was then employed.

Graft Number	Treatment	Volume of Injection	ODN Concentration	Duration of Treatment
1-3	Vehicle (PBS)	50 μ l	-	20 days
4-6	RandomODN#R451	50 μ l	10 μ M	20 days
7-9	ODN#27	50 μ l	10 μ M	20 days
10-12	ODN#74	50 μ l	10 μ M	20 days
13-15	ODN#50	50 μ l	10 μ M	20 days

As determined above, oligonucleotide #27 (ODN #27) reduced IGF-I receptor mRNA *in vitro* to less than 35% of GSV-treated cells. Oligonucleotide #50 (ODN#50) reduced IGF-I receptor mRNA *in vitro* to between 35 and 50% of GSV-treated cells. Oligonucleotide #74 (ODN #74) was not inhibitory to IGF-I receptor mRNA *in vitro*. In the *in vivo* model, each mouse received two grafts. Random oligonucleotide or vehicle was injected intradermally in one graft and acted as a control. The second graft was injected with the targeted oligonucleotide. Each graft received an injection every second day for the duration of the treatment.

Histology of representative grafts from each treatment type are shown in Figures 18(a)-(d) and 19(a) - (d). Each sheet shows three images of H&E stained sections: the pregraft histology, the control treated graft, and the targeted oligonucleotide treated graft. Figures 18(a)-(d) are shown at 100x magnification; figures 19(a)-(d) are shown at 400x magnification. The total cross sectional area of epidermis of each graft was assessed using MCID analysis software. The pooled results from all of the treated grafts are shown in Figure 20.

As shown in Figures 18(a)-(d) and 19(a)-(d), the vehicle-treated (control) grafts were marginally thinner than the pregraft sections. The degree of regression in these

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experiments (ie., less than 10%) is not significant. A similar amount of marginal thinning of epidermis compared to pregraft also occurred in pilot experiments in which psoriatic grafts were not injected, and ~~thus~~^{thus} it is unlikely that the vehicle itself has any effect.

Histological features of psoriasis present in skin samples prior to grafting (clubbing of rete
5 ridges, parakeratosis, acanthosis) were present in these grafts.

The random oligonucleotide treated grafts varied in epidermal thickness after 20 days of treatment. Grafts were either a similar thickness to the pregraft histology, or marginally thinner. Random oligonucleotide treated grafts were in each case significantly thicker
10 than their targeted oligonucleotide treated pairs.

As shown in Figure 20, the targeted oligonucleotide treated grafts were significantly thinner than the pregraft sections and showed less parakeratosis and clubbing of rete ridges. Antisense oligonucleotides which were effective at reducing IGF-I receptor
15 mRNA levels *in vitro* (#27 and #50) produced greater epidermal thinning than an oligonucleotide which was not inhibitory to IGF-I receptor mRNA *in vitro* (#74). Accordingly, there is a direct correlation between the ability of an oligonucleotide targeted to the IGF-I receptor to inhibit IGF-I receptor mRNA levels *in vitro* and the efficacy of the oligonucleotide as an anti-psoriasis agent in an *in vivo* model.

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EXAMPLE 20

Another experiment demonstrated that treatment of psoriatic grafts with an oligonucleotide targeted to a genetic sequence encoding the IGF-I receptor results in inhibition of proliferation. Pregrafts from psoriatic patients, control grafts treated with R4541, and
25 grafts treated with oligonucleotide #27 were obtained as described in Example 19. An antibody to the cell cycle-specific nuclear antigen Ki67 was used to immunohistochemically detect actively dividing cells and ~~thereby~~^{hereby} assess proliferation. The α Ki67 antibody (DAKO, Glostrup, Denmark) recognizes the Ki67 antigen transiently expressed in nuclei of proliferating cells during late G₁, S, M and G₂ phases of the cycle

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Topical formulations of complexes of oligonucleotides with cytofectin GSV in aqueous or methylcellulose gel formulations were prepared and assessed for uptake of the oligonucleotide by keratinocytes *in vivo*. The topical formulations contained
25 oligonucleotides complexed with cytofectin GSV in an aqueous solution or methylcellulose carrier, as taught herein. With both aqueous and methylcellulose gel formulations, localization of oligonucleotide R451 to nuclei and cytoplasm of keratinocytes in normal human skin grafts on nude mice was observed. Figure 22 shows an image from confocal microscopy demonstrating oligonucleotide localization in the nuclei and cytoplasm of

keratinocytes in normal human skin grafts after topical application of fluorescently labeled oligonucleotide (10 μ M R451) complexed with cytofectin GSV (10 μ g/ml). Figure 23 shows an image from confocal microscopy demonstrating that topical application of the same oligonucleotide/GSV concentrations in a 3% (w/v) methylcellulose gel produced similar uptake in the target keratinocyte population. Using an aqueous formulation of oligonucleotide/GSV complexes, penetration of oligonucleotide into the viable epidermis was observed, whereas application of formulations of oligonucleotide complexed with other cationic lipids resulted in localization of oligonucleotide in the stratum corneum.

EXAMPLE 22

Thirteen antisense oligonucleotides targeted to IGFBP-3 were synthesized. The antisense oligonucleotides are C5-propynyl-dU, Dc15 mer phosphorothioate oligodeoxyribonucleotides. Figure 24 attached hereto is a schematic diagram indicating the position of the thirteen oligonucleotides relative to the IGFBP-3 mRNA structure.

These oligonucleotides were screened for their ability to inhibit IGFBP-3 mRNA levels of HaCaT cells in accordance with the teachings herein. HaCaT cells were grown to 90% confluence in DMEM supplemented with 10% (v/v) FCS, then placed in complete keratinocyte serum free medium (KSFM, Gibco), which has a defined amount of EGF, for 24 hours. Oligonucleotides (30nM or 100nM) were complexed with GSV cytofectin (2 μ g/ml) and added to cells in complete KSFM to allow oligonucleotides to enter the nucleus before removal of EGF. Repeat additions were performed at three hours (in serum free DMEM, which releases the EGF inhibition of IGFBP-3 mRNA) and again after another 24 hours. HaCaT cells were also treated with randomized sequence oligonucleotides (R121, R451, R766 and R961), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated as described in Example 17, 24 hours after the last treatment. Total RNA (15 μ g) was analyzed by Northern analysis and phosphoroimager quantitation for IGFBP-3 and GAPDH mRNA. IGFBP-3 mRNA is expressed as the amount of IGFBP-3 mRNA relative to the amount of GAPDH mRNA.

Figures 25(a)-(d) provide graphs which depict results in this screening process. In these graphs, R1 and R12 refer to R121; R4, R4(0) and R45 refer to R451; R7, R7(0) and R76 refer to R766; and R9 and R96 refer to R961. The values were standardized to GSV-treated cells, and data was pooled and statistically analyzed by ANOVA followed by Domet's test to compare each treatment to GSV-treated cells. The pooled data are presented as a bar graph in Figure 26. As demonstrated, at a concentration of 30nM, treatment of HaCaT cells with 8 of the 12 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells. At a concentration of 100nM, treatment with 9 of the 13 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells.

These experiments demonstrate that antisense oligonucleotides targeted to genetic sequences encoding IGFBP-3 can inhibit IGFBP-3 mRNA levels in human keratinocytes *in vitro*.

EXAMPLE 23

IGF-I receptor is a potent mitotic signalling molecule for keratinocytes and the human receptor elicits separate intracellular signals that prevent apoptosis (19). It is proposed in accordance with the present invention that inactivation of IGF-I receptors in epidermal keratinocytes will achieve three important outcomes in subsequent UV treatment of lesions:

- (i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation (22). By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is likely to be reduced leading to an overall acceleration in normalization of the lesion and reduced carcinogenic risk.

(ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.

(iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.

Accordingly, antisense therapy, especially against IGF-I-receptor is useful in combination with UV therapy in the treatment of epidermal hyperplasia.

EXAMPLE 24

HaCaT cells were treated with antisense oligonucleotides directed to IGF-I receptor mRNA. Levels of IGF-I receptor mRNA were then monitored. In essence, confluent HaCaT cells were treated every 24 hours for four days with 2 μ g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides (#26 to #86) or random sequence oligonucleotides (*R121*, *R451* and *R766*). Figure 27(a) is a photographic representation showing representative RNase protection assay gel showing IGF-I receptor (IGFR) and GAPDH mRNA in untreated or treated HaCaT cells. Figure 27(b) is a densitometric quantification of IGF-I receptor mRNA in a HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black) random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells (UT, vertical striped bar).

EXAMPLE 25

In this example, reduction in total cellular IGF-I receptor protein was monitored following antisense oligonucleotide treatment. Confluence HaCaT cells were treated with 24 hours for 4 days with 2 μ g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONS (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with antibody specific for the human IGF-I receptor. Figure 28(a) shows duplicate treated cellular extracts following the IGF-I receptor at the predicted size of 110 kD. Figure 28(b) is a densitometric quantification of IGF-I receptor protein.

EXAMPLE 26

The reduction in IGF-I receptor numbers was determined on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were transfected with IGF-I receptor specific AONs #27, #50, #64, a random sequence oligonucleotides (R451) or following treatment with GSV a lipid alone every 24 hours for 4 days. Competition binding assays using ^{125}I -IGF-I and the receptor-specific analogue, des(1-3)IGF-I were performed. Results are shown in Figure 29.

EXAMPLE 27

In this example, the apoptotic protecting effects of IGF-I receptor on keratinocyte cells was tested by following the reduction in keratino cell numbers following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6414 or treated with GSV a lipid alone every 24 hours for 2 days. The cell number was measured in culture wells using a dye binding assay. The results are presented in Figure 30. The results clearly confirm that the IGF-I receptor exhibits an anti-apoptotic effect. By reducing IGF-I receptor levels using antisense oligonucleotide treatment, the anti-apoptotic effect is interrupted and apoptosis results in the reduction in keratinocyte cell number. Results are shown in Figure 30.

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EXAMPLE 28

This example shows a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides. Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed histologically. The results are shown in Figure 31. In Figure 31(a), donor A graft treated with AON #50 showing epidermal thinning compared with the pregraft and control (PBS) treated graft and donor graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. In Figure 31(b), the mean epidermal cross-sectional area over the full width of grafts is shown as determined by digital image analysis. The results show that epidermal hyperplasia is reversed following the intradermal injection of antisense oligonucleotides.

EXAMPLE 29

Figure 32 shows the reversal of epidermal hyperplasia correlating with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides. Figure 32(a) shows a psoriasis lesion prior to grafting and after grafting and treatment with IGF-I receptor specific oligonucleotide #27 (AON #27) or random sequence (R451) immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are indicated by a dark brown nucleus (arrows). Figure 32(b) shows the same lesion prior to grafting and after oligonucleotide treatment as in Figure 32(a) but subjected to *in situ* hybridisation with ³⁵S-labelled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains which are almost eliminated in the epidermis of the lesion treated with IGF-I receptor specific oligonucleotide # 27 (AON #27). This experiment shows that reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides.

EXAMPLE 30

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Figure 33 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for two days with 2 μ g/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially available ribonuclease protection assay kit. The results show a reduction in IGF-I receptor mRNA in the HaCaT keratinocyte cells.

EXAMPLE 31

Figure 34 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 4 days with 2 μ g/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells were lysed in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v glycerol, 1 v/v Trison X-100 and 100 μ g/ml aprotinin on ice for 30 minutes, then 30 μ g of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane. Membranes were then incubated with anti-IGF-I receptor antibodies C20 (available from Santa Cruz Biotechnology Inc., Santa Cruz, California) for 1 hour at room temperature and developed using the Vistra ECF western blotting kit (Amersham). The results shown in Figure 34 confirm that IGF-I receptor protein is reduced in HaCaT keratinocytes following treatment with oligonucleotides.

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EXAMPLE 32

This example shows a reduction in HaCaT keratinocyte cell number following treatment with oligonucleotides. The results are shown in Figure 35. HaCaT cell monolayers were grown at 40% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 3 days with 2 μ g/ml GSV lipid alone (GSV) or complexed with 15 nM oligonucleotide. Cell numbers were then measured every 24 hours using the amido black dye binding assay [32]. Results show that HaCaT keratino cells decrease in number following treatment with oligonucleotides due to a reduction in the anti-apoptotic effect of the IGF-I receptor.

5 includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

[illegible]

REFERENCES:

1. Sara V *Physiological Reviews* 70:591-614, 1990.
2. Rechler MM and Brown AL *Growth Regulation* 2:55-68, 1992.
3. Clemmons DR *Growth Regn* 2:80, 1992.
4. Oakes SR, KM Haynes, MJ Waters, AC Herington and GA Werther *J. Clin Endocrinol Metab* 73:1368-1373, 1992.
5. Camacho-Hubner C *et al. J Biol Chem* 267:11949-11956, 1992.
6. Neely KE *et al. J Inv Derm* 96:104, 1991.
7. Ts'O POP, Aurelian L, Chang E and Miller PS. Nonionic oligonucleotide analogs (Matagen TM) as anticodic agents in duplex and triplex formation. in "Antisense Strategies", Annals of the New York Academy of Sciences 660:159-177 (Baserga R and Denhardt DT, eds.), 1993.
8. Haseloff J and Gerlach L *Nature* 334:586-591, 1988.
9. Boukamp P, Petrussevska RT, Breitkreuz D, Hornung J, Markham A, Fusenig NE. *J Cell Biol* 106:761-771, 1988.
10. Rheinwald and Green *Cell* 6:331-344, 1975.

- 122 -

11. Hossenlopp P, Seurin D, Segovia-Quinson B, Hardouin S, Binoux M. *Anal Biochem* **154**:138-143, 1986.

007292 46295560

12. Spratt SK, Tatsuno GP, Yamanaka MK, Ark BC, Detmer J, Mascarenhas D, Flynn J, Talkington-Verser C, Spencer EM. *Growth Factors* 3:63-72, 1990.
13. Pietrzkowski, Z, Sell C, Lammers R, Ullrich A and Baserga R. *Mol. Cell. Biol.* 12: 3883-3889, 1992.
14. Schulz J, Dettlaff S, Fritzsche U, Harms U, Schiebel H, Derer W, Fusenig NE, Hulsen A and Bohm M. *J. Immunol. Meth.* 167:1-13, 1994.
15. Baker BS, Brent L, Valdimarsson H, Powles AV, Al-Imara L, Walker M and Fry L. *Brit. J. Dermatol* 126:105-110, 1992.
16. Nanney LB et al *J. Invest. Dermatol* 98:296-301, 1992.
17. Sundberg JP et al *Immunol. Investigations* 22:389-401, 1993.
18. Sundberg JP et al *J. Invest. Dermatol* 102:781-788, 1994.
19. O'Connor et al *Mol Cell Biol* 17:427-435, 1997.
20. Kuhn et al *Int J Cancer* 80:431-438, 1999.
21. Resnicoff et al *Cancer Res* 55:3739-3741, 1995.
22. Ouhtit et al *Am J Pathol* 156:201-207, 2000.
23. Froehler et al *Tetrahedrin Lett* 34:1003-1006, 1992.

24. Gennaro (Ed) *Remington's Pharmaceutical Sciences* 18th Edition Mack Publishing Co., Easton PA USA, 1990.
25. Flanagan *et al Nat Biotechnol* **14**:1139-1145, 1996.
26. Flanagan *et al Nucleic Acids Res* **24**:2936-2941, 1996.
27. Flanagan *et al Mol Cell Biochem* **172**:213-225, 1997.
28. Gutierrez *et al Biochemistry* **36**:743-748, 1997.
29. Moulds *et al Biochemistry* **34**:5044-5053, 1995.
30. Wagner *et al Science* **260**:1510-1513, 1993.
31. Wagner *et al Nature* **372**:333-335, 1994.
32. Schultz *et al J Immunol Meth* **167**:1-13, 1994.